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EFFECTS OF REWARDING AND PUNISHING INTRACRANIAL
STIMULATION ON HIPPOCAMPAL ELECTRICAL ACTIVITY

by



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A THESIS

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Effects of Rewarding and Punishing Intracranial Stimulation on Hippocampal Electrical Activity", submitted by Orestes Fedora in partial fulfillment of the requirements for the degree of Master of Science

Abstract

The present study was designed to compare two methodologies in evaluating the effects of electrical stimulation of the lateral hypothalamus on hippocampal electrical activity. In addition, the effects of stimulation of the dorsal tegmentum were also investigated. Half of the lateral hypothalamic Ss were trained five days in a self stimulation paradigm and five days in an escape paradigm while the other half received the training in the reverse order. The dorsal tegmentum Ss were trained 14 days in an escape paradigm. Hippocampal activity during self stimulation consisted mostly of low amplitude, high frequency theta, although large amplitude high frequency theta or desynchrony were also observed. This wide variation in hippocampal activity accompanied a wide variation in self stimulation behavior. Hippocampal activity during lateral hypothalamic escape training consisted mostly of high amplitude, high frequency theta which accompanied the elicited locomotor exploratory behavior. Hippocampal activity during dorsal tegmentum escape training consisted of large amplitude theta waves throughout the session. The highest frequency theta occurred during the running behavior elicited by tegmental stimulation, with a lower frequency theta accompanying the termination of running during the post-stimulatory interval. The lowest frequency theta was observed after an escape response. The results of the present study were consistent with the hypothesis that hippocampal theta is a correlate of motor activity.

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Introduction

The structures of the rhinencephalon or limbic lobe were long neglected and considered to be mainly concerned with olfaction. Rose (1927) challenged the concept that the hippocampus was concerned with olfactory mechanisms and, in 1933, Herrick suggested that the hippocampal primordium was an important region for complex behavior and for the integration of impulses arriving from the brain stem. The real turning point in studies of the rhinencephalon and behavior came when Klüver and Bucy (1937) demonstrated that bilateral temporal lobectomy in monkeys gave rise to a bizarre behavioral syndrome. This syndrome, now labeled the Klüver Bucy syndrome, consists of changes in emotional and discriminative behavior and in sexual and dietary habits.

Papez (1937) excited considerable interest in the rhinencephalon when he suggested that the limbic structures played a role in emotion. He proposed a circuit which passed successively from hippocampus to fornix, mammillary body, anterior thalamus, back to the cortex and through the gyrus cinguli to the hippocampus once more. This proposed circuit received much attention from neurologists and neurophysiologists even though it was demonstrated that a fornix section in man (breaking the circuit) produced few behavioral changes (Heath, 1951).

One of the more dominant ideas of hippocampal function emerged from examination of human patients with large temporal lobe lesions (Douglas, 1967). Damage to this area of the brain was often found to

produce striking memory deficits. The deficit, termed a loss of recent memory (i.e., memory since operation), consists of an inability to correctly recall events a few minutes after they have occurred (i.e., loss of long term memory), coupled with an intact ability to recall events which occurred before the operation. The association of the hippocampus with this defect has a long history (Stepien & Sierpinski, 1964), but decisive evidence for this idea was not available until completion of the investigations of Scoville and Milner (1957) and Penfield and Milner (1958).

As early as 1940, Renshaw, Forbes, and Morrison pointed out that the morphology of the hippocampus provides a very suitable model for the study of the electrogenesis of evoked potentials and spontaneous waves, since the cell bodies were arranged in almost ideally stratified layers. Although large amplitude, 5-7 Hz, regular waves (theta rhythm) were incidently observed by Gerard, Marshall, and Saul (1936), it was Jung and Kornmüller (1938) who first discovered that peripheral stimuli could change the spontaneous hippocampal activity to one of synchronous theta rhythm. Theta rhythm was also noted in later studies (Liberson & Akert, 1953; Green & Arduini, 1953).

Anatomy and physiology of the hippocampus. The hippocampal formation is a comma shaped archipallial structure occupying a considerable portion of each cerebral hemisphere. Its principle parts are the fornix, dentate gyrus, hippocampus proper, subiculum, presubiculum, and entorhinal cortex. Although distinct from an anatomical standpoint,

the subiculum, presubiculum, and entorhinal cortex are hard to distinguish physiologically. The hippocampus proper consists of seven layers, with the pyramidal cell body located in the fourth layer. The fimbria is continuous with the fornix and is composed essentially of afferent and efferent fibers. The afferent fibers terminate on the CA3-4 pyramids and granule cells of the dentate gyrus. The dense layer of granule cells forms an interlocking C with the inverted C of the hippocampal pyramids (Green, 1964).

The two major afferent inputs to the hippocampus are the septo-hippocampal circuit (S-H) and the temporoammonic circuit (T-A). The S-H circuit carries impulses from the septal region through the fornix to the CA3 and CA4 pyramids, and to a lesser extent, the densely packed dentate granule cells. The dentate granule cells, in turn, send axons to terminate on apical dendrites close to the soma of the hippocampal pyramids (Raisman, Cowan, & Powell, 1965). Those subcortical structures which send dominant projections to the hippocampus do so via the S-H circuit (Green, 1964). Theta rhythm does not occur unless septal-hippocampal connections are intact. Theta rhythm is paced by rhythmically firing cells, called B-units, located in the septal region. The axons of the B-units synapse on the dentate granule cells (Petsche, Gogolak, & van Zwieten, 1965; Petsche, Stumpf, & Gogolak, 1962).

Concerning the genesis of the hippocampal theta rhythm, Andersen, Brooks, and Eccles (1964), Andersen and Eccles (1962), and Spencer and Kandel (1961) stress the importance of recurrent inhibitory circuits.

This model necessitates activation of basket cells via hippocampal pyramid collaterals. Once activated, the basket cells would hyperpolarize the pyramidal cells, producing IPSPs. Thus, in this model, the theta rhythm is simply a result of the synchronous IPSPs in adjacent cells. Fujita and Sato (1964) reported synchronous intra- and extra-cellular theta range fluctuations. However, the intracellular fluctuations appeared to be EPSPs rather than IPSPs. The data of Fujita and Sato strongly suggests that theta rhythm is the result of synchronous EPSPs even though the researchers could not totally rule out the presence of IPSPs.

The major T-A afferents consist of fibers which pass through the subiculum, terminating on the hippocampal pyramids and granule cells. The terminal arborizations of these fibers make contact with the dendritic plexus of the apical dendrites and, less profusely, with the dendritic field of the granule cells of the fascia dentata (Raisman, Cowan, & Powell, 1965). This apical dendritic system is essentially an excitatory system for activation of hippocampal pyramids (Andersen & Lømo, 1970).

Nauta (1956) has summarized the connections of the two major efferent pathways from the hippocampus. Axons of the hippocampal pyramids divide to form the two efferent projections; one subdivision is directed to the fimbria and fornix, the other subdivision is directed oppositely, towards the subiculum. The efferents which pass through the fimbria and fornix directly connect with (a) all septal cell groups

via the precommissural or postcommissural fornix, (b) the preoptic area via the precommissural fornix, (c) hypothalamic areas which spread mainly over the dorsal region and the periventricular zone of the hypothalamus, (d) the anterior thalamic nucleus, the median nucleus, and the paramedian nucleus of the thalamus via Gudden's bundle, and (e) the medial and lateral nuclei of the mammillary body, and, to a lesser extent, with the supramammillary body. In addition to the above direct connections, the influence of impulses generated in the hippocampus is extended through the connections of the nuclei receiving afferents from the hippocampus.

Electrophysiological studies have demonstrated connections from the hippocampal pyramids to the entorhinal cortex (Adey, Dunlop, & Sutherland, 1958). Anatomical evidence (Ramón y Cajal, 1909) indicates the presence of efferents directed toward the entorhinal cortex; it is not clear, however, whether these efferents do, in fact, terminate directly in the entorhinal cortex.

Hippocampal lesion effects on behavior. Both the memory loss idea and studies of hippocampal theta activity had the effect of stimulating animal lesion research. Although hippocampal lesions in animals began as early as 1930, this research did not have a continuous history to the present day. A great deal of the recent research on the behavioral effects of hippocampal lesions stems from work begun in the Isaacson laboratory as late as 1959 (Isaacson, Douglas, & Moore, 1961). The recent review by Douglas (1967) on the relation of the hippocampus to

behavior has been the primary source for the following summarization of hippocampal lesion effects on behavior.

One of the most useful ideas that emerged from a consideration of the animal lesion data was that hippocampectomy might produce an inability to withhold a response (perseveration). It was repeatedly found that the hippocampectomized animals excel over normals on tasks in which a disruptive response inhibition is present, are normal on tasks in which no response inhibition is involved, and are inferior to normals on tasks requiring response inhibition. Thus, hippocampal rats are superior, as compared with normals on a two-way active avoidance task and either no different or slightly deficient, as compared with normals, in a one-way active avoidance task. The difference between two-way and one-way active avoidance tasks has been explained in terms of a disruptive passive avoidance tendency in the two-way task which is absent in the one-way task and in hippocampectomized animals. Other tasks in which a disruptive inhibitory tendency is present (resulting in superior performance by hippocampectomized animals) are enforced start box delay tasks and tasks where previously trained Ss are exposed to distracting tactile or visual stimuli.

The tasks most frequently used in testing hippocampectomized animals are those demanding inhibitory tendency (which is absent in Ss with hippocampal lesions). Thus, hippocampal lesions produce extinction, passive avoidance, and CER deficits in rats. Hippocampal animals are also inferior, compared to normals in various types of alternation

tasks. Animals with hippocampal lesions are unable to make alternate responses to two stimuli or to switch the response from one of holding down a lever to one of pressing and releasing it and vice versa. Hippocampectomized rats also show a deficit when switched from a continuous reinforcement schedule to non-continuous schedules (DRL, $S\Delta$, & VI). Hippocampal rats are able to learn a DRL schedule if they are not pre-trained on a continuous schedule.

Hippocampal lesions also result in deficits in maze learning and successive discrimination. An analysis of the animals' behavior reveals that hippocampectomized rats repeatedly re-entered blind alleys in multiple T-mazes, lacked flexibility in their choices of pathways in a Dashiell maze, and lacked the normal tendency of the rat to avoid entering the same alley of a T-maze on two consecutive trials (spontaneous alternation). Thus, the maze learning deficit of hippocampectomized rats can be explained as being due to the lack of a normal ability or tendency to avoid alley re-entry when the response is unreinforced. In a successive discrimination task, normal rats invariably develop a strong turning habit which is then abandoned just prior to an improvement over chance success on the task. Since hippocampectomized rats never abandon their turning habit, the deficit they show on this task can be explained as due to the lesioned S's inability to inhibit the prepotent turning habit (Douglas, 1967).

The absence of a drop in performance by hippocampectomized rats of a runway task when a distracting stimulus is introduced has led to

the suggestion that hippocampal lesions produce a deficit of the orienting response. Hendrickson and Kimble (1969), however, have found that hippocampal lesions do not affect a rat's orienting response to a single stimulus but do affect the rat's ability to shift the orienting response to a second stimulus when two stimuli are present at once.

Although the response perseveration hypothesis is successful in the analysis of the hippocampal lesion data, Douglas (1967) points out the difficulties of attempting to define what constitutes a "response" and explaining why the response does not perseverate in the absence of the appropriate stimuli. He suggests an alternative hypothesis which avoids the difficulties of the response perseveration hypothesis; he suggests that the hippocampus may inhibit bonds, connections, or associations between stimuli and responses (Douglas, 1967). Douglas' hypothesis is functionally similar to a hypothesis suggested by Kimble (1968); that the hippocampus mediates Pavlovian internal inhibition. Both hypotheses, in addition to handling the lesion data, can explain why the response does not perseverate when response inducing stimuli are absent.

Hypotheses concerning the functional significance of theta.

Several hypotheses have been proposed to elucidate the possible significance of hippocampal theta rhythm and its relation to functions performed by the hippocampus in mediating behavior.

One of the earliest studies of hippocampal theta activity was made by Green and Arduini (1954). These authors elicited hippocampal

synchronous waves in acute preparations of unanesthetized rabbits, cats, and monkeys. These wave forms were found in Ss immobilized either by tubocurarine or by midbrain transection, as well as chronic preparations of rabbits and monkeys. Hippocampal theta, whether elicited by any one of a variety of afferent stimuli, or by direct excitation of the activating mechanisms in the brainstem was almost always associated with cortical EEG desynchronization. Green and Aruini (1954) interpreted this finding as support for their hypothesis that theta activity was a "specialized paleocortical arousal reaction".

Grastyán, Lissak, Madarasz, and Donhoffer (1959) investigated the role of hippocampal theta in a series of conditioning studies involving instrumental approach and avoidance tasks. Cats with dorsal hippocampal and neocortical electrodes served as Ss. The approach task involved presenting an auditory stimulus which signaled the presence of a food reward on a shelf above the S's head. The avoidance task involved an auditory stimulus signaling the onset of shock in a two-way active avoidance box. In contrast with the findings of Green and Arduini (1954) they found that the initial presentation of the CS in either task resulted in both neocortical and hippocampal desynchronization (Grastyán et al., 1959). Only after the auditory stimulus was paired several times with food or shock delivery did hippocampal synchronization (theta) appear in response to the CS presentation. When, with further training, the approach or avoidance response was elicited consistently in the presence of the discriminatory stimulus, the hippocampal activity

reverted to desynchrony. Initiating extinction trials or changing the pitch of the auditory CS during the latter stages of training was found to reinstate hippocampal synchrony.

When the hippocampal activity was compared with motion pictures of the concomitant behavior of the animals during training, it became obvious that the hippocampal theta waves were always associated with overt behavioral orienting toward the source of stimulation. Overt orienting responses were not made during the initial CS presentations, but only appeared after the auditory stimulus was paired several times with the food or shock. As training continued, the behavioral orienting to the discriminative stimulus diminished and finally disappeared. The initiation of extinction trials or a change in the pitch of the stimulus reinstated orienting behavior during the latter stages of training.

Grastyán et al. (1959) argued that synchronous slow wave activity may represent a depressed or relatively inactive state in both the hippocampus and the neocortex, whereas fast wave activity may represent an activated state of both areas. Grastyán also concluded that hippocampal desynchrony is responsible for the inhibition of the orienting reflex, possibly by inhibiting the reticular formation and the hypothalamus. Thus, Green and Arduini (1954) proposed that theta represents an active state of the hippocampus, while Grastyán et al. (1959) proposed the opposite.

Adey and his co-workers (Adey, Dunlop, & Hendrix, 1960; Holmes & Adey, 1960) have reported recording theta rhythm from the hippocampus

which seemed to be correlated with approach behavior, rather than orienting behavior. Holmes and Adey (1960), using a delayed response situation, trained cats to choose one of two elevated pathways leading to goal boxes alternately baited in the presence of the animal. Even before training, slow 4-6 Hz theta waves were recorded from the entorhinal cortex whenever the cats appeared to be alert or attentive. As training proceeded, the entorhinal theta activity tended to appear more and more briefly during the delay period preceding the opportunity to respond. When S was permitted to respond, a bridge was lowered, so that S could approach the goal box. During this period of time the entorhinal record contained a burst of high amplitude theta waves at 6 Hz, which continued to occur well after the CR was established. During extinction of the CR no bursts of theta occurred (after the bridge was lowered) in the habituated S, although 4-5 Hz activity continued to occur during the delay period just preceding the lowering of the bridge. On retraining, 6 Hz bursts rapidly reappeared during the opportunity to approach the goal box.

Adey, Dunlop, and Hendrix (1960) implanted cats with chronic electrodes in CA1-4 areas of the hippocampal pyramids, in the entorhinal cortex, and in the amygdala. They recorded electrical activity from the implanted areas while the animals were performing a simultaneous two-choice visual discrimination task. Close inspection of photographic and EEG records revealed that the 5.5 to 6.5 Hz bursts in the dorsal hippocampus and entorhinal cortex occurred only during motor activity

of the subject. If the animal made an incorrect response, and corrected it, bursts appeared during the performance of both responses, but did not appear during the period of motor inactivity between the two approaches. Adey et al., also observed that during the choice point period, the animal often turned his head from side to side as though searching "in a fashion strongly reminiscent of classical descriptions of the orienting reflex". Theta activity did not appear during this searching behavior.

Adey and his associates concluded that theta activity is a correlate of the alert state found in "goal-directed motor activity". However, because theta appeared in the absence of overt movement (that is, both spontaneously and during the extinction of approach responding) they concluded that theta "indicates a readiness to act".

Bremner (1964) attempted to determine whether hippocampal theta activity was a correlate of centrally initiated attention or arousal, or a hippocampal response to the occurrence of an orienting response. He also investigated the effect of disrupting theta activity during the performance of an overt response (conditioned avoidance). Bremner found that the dorsal hippocampal response of rats in a Sidman avoidance task changed from desynchrony to regular 5-7 Hz activity just preceding and during a lever press. This change from hippocampal desynchrony to synchrony continued for hundreds of trials. Since theta rhythm was found in the absence of an exteroceptive warning stimulus and since it did not extinguish (as would be expected of an orienting response), Bremner concluded that hippocampal theta is not a correlate of the orienting response.

Disruption of the theta rhythm with electrical stimulation of the hippocampus (below seizure level) did not interfere with the performance of the conditioned avoidance response. Bremner concluded that hippocampal theta results from centrally initiated attention or arousal, but is not, in itself, a necessary concomitant of arousal or responding, at least not in the instrumental avoidance of shock. Bremner also pointed out that in the two-choice visual discrimination task used by Adey et al. (1960), the animals certainly had to be attentive to cues in order to respond correctly. Unfortunately, the tasks used by Adey et al., and Bremner both confound goal directed motor activity and arousal.

In cats with chronic implanted electrodes, Grastyán, Karmos, Vereczkey, Martin, and Kellenyi (1965) recorded electrical activity from the dorsal hippocampus during electrical stimulation of the hypothalamus. Hypothalamic stimulation was initiated by E and could be turned off if the animal pressed a bar. In most of the hypothalamic regions, repeated stimulation (with current of moderate intensity) elicited orienting behavior: sniffing and searching accompanied by progressively increasing locomotion and, simultaneously, a continuous and regular theta rhythm in the hippocampus. The cats avoided pressing the bar which suggests stimulation was positively reinforcing. In response to a stepwise increase in the intensity of the current, both the behavioral and electrical manifestations of stimulation gradually changed until, on reaching a critical intensity, they were in sharp

contrast with the earlier results. Orienting movements were replaced by ever-increasing, flight-like running and the former theta rhythm was gradually displaced by desynchronization in the hippocampus. During hippocampal desynchronized activity, the subjects learned to press the bar shortly after onset, which suggests that the stimulation was punishing.

Stimulation of some hypothalamic points did not produce a change from positive to negative reinforcement with increasing stimulation intensity. Stimulation of these points with widely different parameters produced effects that varied in intensity but were always of the same type. Points producing only theta activity and movements of an orienting type were found in the lateral hypothalamic (LH) area. Points producing exclusively crouching and withdrawing movements simultaneously with hippocampal desynchronization were found in the medial hypothalamic (MH) and perifornical area.

Ito (1966) using self-stimulation in the rat investigated the relationship between intracranial stimulation (ICS) and hippocampal electrical activity. Each rat carried two subcortical electrodes for stimulation and one for recording hippocampal activity. Three types of changes in the hippocampus were observed during stimulation of several subcortical points: (a) synchronization or theta rhythm, (b) attenuation or suppression of slow wave activity, and (c) 30-40 Hz activity. Hippocampal synchronization could be evoked most clearly with stimulation of the midbrain reticular formation (MRF) and the MH area and was

correlated mainly with attentive-like behavior, sniffing or searching behavior. Attenuation of hippocampal activity amplitude was in most cases elicited by septal stimulation. The 30-40 Hz activity (labeled desynchrony by Ito) was predominantly produced by LH and lateral pre-optic stimulation and was correlated with running and violent vocalization. Electrical stimulation which produced fast wave activity (30-40 Hz) had mixed effects on bar pressing rates. Some areas induced self stimulation, others inhibited it, while still others had ambivalent effects. Electrical stimulation which produced synchronization did not induce self stimulation.

Ito and Grastyán both concluded that orienting behavior is correlated with theta activity. They disagree, however, on the relationship of hippocampal activity to the reinforcing properties of the ICS. Ito's data suggest a correlation between desynchrony and positive reinforcement and between synchrony and negative reinforcement. Grastyán's data suggest precisely the opposite. The discrepancy between the studies of Ito and Grastyán could be attributed to a species difference and/or differences in electrode placement. However, there were also differences in procedure which could have influenced the results. In the study by Grastyán et al., E turned on the ICS and S turned it off by pressing a bar. In the study by Ito, S turned the ICS both on and off with a bar press. However, Ito, in determining voltage levels, did turn on the LH ICS and still found desynchronization. Torii (1961) found, in unanesthetized rabbits immobilized by tubocurarine, desynchronization

of the hippocampus was elicited by direct stimulation of the LH. While these results are contradictory to those of Grastyán et al. (1965), it should be pointed out that in the studies by Ito and Torii, the stimulation was on for only a short duration and no investigation was carried out of the effects of prolonged stimulation of the LH over a number of trials.

The purpose of the present experiment is to replicate part of Ito's study with rats, but, in addition, subject the LH rats to the procedure employed by Grastyán. To avoid mixed effects of electrical stimulation, electrode placement will be aimed at primarily positively reinforcing centers and negatively reinforcing centers (Olds & Olds, 1964).

Method

Subjects. The Ss were twenty-four male Wistar rats weighing 240 to 290 gm. twenty-four hours prior to surgery.

Surgery. Electrode implantation was performed under pentobarbital sodium anesthesia (60 mg/kg) injected intraperitoneally after 24 hours of food deprivation (Routtenberg, 1968). Atropine sulfate (0.4 mg/kg) was injected intraperitoneally ten minutes prior to the anesthetic. The general anesthetic was supplemented by a local subcutaneous injection of Xylocaine. Neosporin was applied topically to the wound area upon completion of electrode implantation.

All Ss were implanted with an electrode assembly containing one or two bipolar stimulating electrodes and a bipolar recording electrode. All electrodes were constructed from 0.01 in. stainless steel wire (Diamel coated) with the insulation removed only from the cross section at each tip. The stimulating electrodes consisted of two wires cemented together with Epoxylite and with the tips cut at a 45° angle. The recording electrodes consisted of two wires equal in length, with the tips cut at a 90° angle and separated approximately 1.4 mm. The stimulating and recording electrodes were connected to a modified Amphenol connector (model 223-1209) prior to surgery, and the entire electrode assembly was implanted as a unit. The electrode assembly was secured to the skull by means of four stainless steel screws and dental cement, with the right frontal screw serving as a ground electrode. In all Ss the recording electrode was implanted in the anterior dorsal

hippocampus on the left side. It was intended that the recording electrode be placed in the CA4 area of the hippocampal pyramids (Adey et al., 1960) using the coordinates: 6.2 mm. anterior, 1.0 mm. lateral, and 1.2 mm. above horizontal zero, for the anterior electrode and 5.2 mm. anterior, 2.0 mm. lateral, and 1.2 mm. above horizontal zero, for the posterior electrode (König & Klippel, 1963). In eleven Ss a single stimulating electrode was implanted in the right lateral hypothalamus using the following coordinates: 4.0 mm. anterior, 1.0 mm. lateral, and 3.8 mm. below horizontal zero. In eight Ss a single stimulating electrode was implanted in the dorsal tegmentum using the following coordinates: 1.2 mm. anterior, 1.5 mm. lateral, and 0.5 mm. above horizontal zero. Four of these electrodes were in the right dorsal tegmentum and four were in the left dorsal tegmentum. In five Ss a pair of dorsal tegmentum stimulating electrodes were implanted bilaterally. These bilateral electrodes were connected in parallel.

Histology. After completion of behavioral testing, Ss were deeply anesthetized with pentobarbital sodium and an anodal current of 50 μ A. was passed through each electrode tip for a duration of 30 seconds. The Ss were then perfused intracardially with normal saline followed by a 10 percent Formalin solution containing 3 percent potassium ferrocyanide. The brains were sectioned on a freezing microtome at a thickness of 50 μ . Microscopic examination and photographs of the unstained sections were made on a dark background, illuminated from the side.

Apparatus. The test apparatus consisted of an electrically shielded plexiglas enclosure, 7 in. wide, 6 3/4 in. deep, and 26 in.

high. Two Lehigh Valley retractable levers were placed 3 1/4 in. apart and 1 1/2 in. above the floor on one wall of the enclosure. The retractable levers were equipped with plexiglas bars which were fitted with minature bulbs (12 VDC, 1.2 w.) which were programmed to illuminate the levers when the levers were extended into the chamber. The main source of illumination in the chamber was provided by a bulb (12 VDC, 6 w.) surrounded by frosted glass and mounted between the two retractable levers. A mercury pool commutator (Mundl, 1967) mounted 32 in. above the chamber floor allowed freedom of movement to Ss and permitted artifact free recording of hippocampal activity. The Ss were connected to the commutator by means of Microdot "mininoise" cables. The entire enclosure was housed in a sound attenuated compartment containing a one-way mirror permitting viewing of the subject while in the apparatus.

Electrical stimulation was produced by a Tektronix 162 waveform generator and a Tektronix 161 pulse generator which was connected to S through an isolation transformer. Stimulation consisted of trains of 0.1 msec. pulses at a rate of 100 Hz. The amplitude of the pulses could be varied from 0-25 volts. The negative pole of stimulation was always the deeper tip of the bipolar electrode implanted in the animal.

A Grass P511 preamplifier, with a half amplitude bandwidth of 0.15 Hz to 30 KHz, and a Thermionic model TP3000 FM tape recorder were used to record the hippocampal activity.

Procedure. All Ss were placed on an ad. lib. feeding schedule for the duration of the experiment. Pre-training, intensity testing,

and training sessions were conducted at night, after a 2-3 week recovery period.

The seven day pre-training procedure involved: (a) habituation of Ss to the apparatus, and (b) elimination of Ss from which theta rhythm (the dependent measure) could not be obtained. During habituation trials, Ss were placed in the experimental chamber with the cable connected to the head, and both levers of the experimental chamber retracted. Duration of pre-training trials was 20 min. for days 1-5 and 1 hr. on days 6 and 7. On day 1 of pre-training, samples of hippocampal electrical activity were tape recorded and on days 2 through 7, hippocampal activity was monitored on a cathode ray oscilloscope. If Ss did not show theta activity during exploration of the chamber, or if there was a poor signal to noise ratio, they were eliminated from the experiment. Thus, two LH Ss and two bilateral DT Ss were eliminated.

All Ss received one day of intensity testing after the pre-training period. The S was placed in the apparatus for one hr., with both levers retracted, and closely observed by E while ICS was delivered to determine each S's threshold voltage. Threshold was defined as the lowest voltage which would reliably elicit an arousal reaction (i.e., raising head, pricking ears, sniffing, looking about, etc.) Hippocampal activity was recorded prior to, during, and after each train of stimulation. The procedure for delivering ICS differed slightly for the LH Ss and the DT Ss.

The ICS for LH Ss was delivered at 10 different intensities, beginning with 2 volts, with successive 2 volt increments to a maximum of 20 volts, when possible. The ICS for DT Ss began at 1 volt, with successive 1 volt increments which were terminated when the ICS first elicited violent escape behavior (bursts of running and/or jumping). At each tested voltage setting, all Ss received at least three trains of 0.5 sec. duration spaced at approximately 10 sec. intervals, with the last train duration, for LH Ss only, extended beyond 0.5 seconds. An attempt was made to initiate the stimulation at each tested voltage only when Ss were not actively exploring the chamber. While this proved feasible for all DT Ss, it was not always possible for some LH Ss.

Both LH self stimulation training and LH escape training consisted of placing S in the apparatus one hour daily for five days. Both levers were retracted for the first and last five minutes of the hour. On days 1-3 of self stimulation training and days 1-3 of escape training, one of the levers was extended during the remaining 50 minutes. Lever A was extended during self stimulation training, while lever B was extended during escape training. On days 4 and 5 of self stimulation training and days 4 and 5 of escape training, the remaining 50 minutes was divided into 4, 5, or 6 equal intervals. Each interval was begun by an extension of the appropriate lever (A for self stimulation, B for escape), terminated by a retraction of the lever, and separated from the next interval by a 30 sec. period with both levers retracted. For both training conditions, lever retraction terminated delivery of ICS.

During self stimulation training, pressing lever A resulted in a pulse train delivered to the LH site which terminated when the lever was released or after 0.5 sec.; in the latter case, the lever had to be released before another train could be initiated. Operant shaping of lever pressing behavior occurred during the first 5-15 minutes of self stimulation training on day one only. The self stimulation voltage was individually adjusted for each S at a level which reliably produced an overt behavioral response, which was, for most Ss, the same as the threshold voltage determined during intensity testing. Most Ss started self stimulating within five minutes of the start of training on day one. All Ss were self stimulating at the end of the first day of training. Days 2 and 3 of self stimulation training were identical to day one except that no shaping technique was used. The self stimulation behavior was monitored throughout the 50 minute period of days 1-3 and if S did not maintain responding behavior, the voltage was increased. During the 4, 5, or 6 intervals of days 4 and 5 of self stimulation training, the voltage was successively increased, from a value below the threshold value to double the threshold value when possible (20 v. max.). During each extension of lever A on days 1-5, S was primed (noncontingent, 0.5 sec. ICS) several times if he did not press the lever within 30 secs. Lateral hypothalamic self stimulation training was followed by another day of intensity testing.

During escape training, extension of lever B initiated a continuous train of LH stimulation which could be terminated for 10.5 seconds

when S pressed the lever. The ICS resumed upon completion of the 10.5 second escape interval. Operant shaping of escape behavior was employed during the first 5-15 minutes of day one only. The voltage of the continuous train for days 1, 2, and 3 was the S's threshold voltage as determined during intensity testing. During the 4, 5, or 6 intervals of days 4 and 5 of escape training, the voltage was successively increased, from a value below the threshold value to double the threshold value when possible (20 v. max.). Lateral hypothalamic escape training was followed by another day of intensity testing.

Five LH Ss received the self stimulation training followed by the escape training while four LH Ss received the training in the reverse order. During each training session, the hippocampal activity was recorded at the beginning and end of each session on days 1, 2, and 3 and for a portion of each interval on days 4 and 5.

Dorsal tegmentum escape training consisted of placing S in the apparatus one hour daily for fourteen days. Both levers were retracted for the first and last five minutes of the hour; during the remaining 50 minutes, lever B was extended. Lever B operated as described in LH escape training, with a 10.5 sec. escape interval on days 1 through 11 and a 20 sec. escape interval on days 12 through 14 of training. Unless lever pressing occurred, S received a continuous series of stimulus trains of 0.5 sec. duration, recurring at a rate of once per second. The recurring stimulus train started when lever B was extended and terminated when lever B was retracted. Shaping procedures were not used

for DT escape training; instead, the ICS voltage was increased until bursts of running in S were produced reliably. This procedure resulted in S learning to escape by pressing lever B with some portion of his body. The voltage which produced the desired behavior varied, requiring slight increases within and between daily sessions for some Ss. The mean threshold voltage for all DT Ss was 4.0 volts and the mean escape voltage on day 14 of training was 6.7 volts. Hippocampal electrical activity was recorded during the first and last 10-15 minutes of each 50 minute training session. Dorsal tegmentum escape training was followed by another day of DT intensity testing.

One bilateral DT S died during training and one ipsilateral DT S and one contralateral DT S did not complete training due to electrode assembly damage.

Power spectra analysis. Randomly selected samples of FM recorded hippocampal electrical activity were first filtered (Kron-Hite bandpass filter, model 330-A, band setting 0.02-50 Hz) and then converted from analog to digital form with a TMC computer of average transients. Hippocampal activity containing spike artifacts was rejected.

During the LH self stimulation condition, hippocampal activity was sampled during ICS and during the 5 min. interval prior to ICS. The 10 sec. samples of hippocampal activity during LH ICS consisted of 20 discrete, 0.5 sec. duration samples abutted together. The 0.5 sec. samples were rejected if the ICS was not on during the full 0.5 sec. duration. On days 4 and 5 of self stimulation training, most of the

hippocampal samples were 5 sec. instead of 10 sec. due to the lack of adequate durations of FM recordings. The 10 sec. samples of hippocampal activity prior to ICS consisted of 10 discrete, 1.0 sec. duration samples abutted together.

During the LH escape condition, hippocampal activity was sampled during ICS as well as during the escape interval with sampling procedures identical for both conditions. The 10 sec. samples of hippocampal activity consisted of 2 discrete 4 sec. duration and 1 discrete 2 sec. duration samples abutted together.

Samples were gathered under three conditions during DT escape training. Twenty samples of 1 sec. duration hippocampal activity were randomly selected consisting of 0.5 sec. duration ICS followed by 0.5 sec. of no ICS. The 1 sec. samples were then divided in half and the initial portions abutted to yield 10 sec. of hippocampal activity during DT ICS. The remaining portions were abutted to yield 10 sec. of hippocampal activity during the post-stimulatory period. The third type of sample was randomly selected from hippocampal activity during the 10 and 20 sec. escape intervals in the same manner as those samples selected during LH escape intervals.

The "BMD02T" program (Dixon, 1970) was used to compute the spectral analyses. The number of lags used for all computations was 100 and the constant time interval for all computations was 0.01 sec. (digital sampling rate of 100/sec.), resulting in a power spectra resolution of 0.5 Hz. The smaller number of total data points for the 5 sec.

samples resulted in a decrease in the statistical dependability of the power spectra estimate (Blackman & Tukey, 1959, p. 21).

The "BMD02T" power spectra estimates were converted to percentage power estimates to allow for between subject comparisons. Percentage power estimates were computed by dividing the power estimate calculated for each 0.5 Hz interval by the total power estimate. Converting digital scores to deviations about the mean of each discrete sample prior to computing power spectra removed large DC shifts between abutted samples; however, this technique did not remove DC trends within discrete samples. These within DC trends, when present, were interpreted by the program as slow periodic waves and resulted in an inflation of the power estimates at low frequencies (below 2 Hz). Therefore the total power estimate used in calculating the percentage power for each sample was the sum for 3.5 to 50 Hz rather than 0.0 to 50 Hz.

Results

LH stimulation. Short duration (0.5 sec.) stimulation during intensity test days and during self stimulation training had similar effects on hippocampal activity. The most frequent effect of LH ICS, at or above threshold intensities, was an amplitude attenuation of slow wave components with no increase in fast wave activity (Figs. 1A-D; 2A-E). The power spectrum analyses during self stimulation training confirmed the presence of theta rhythm and the absence of fast wave activity during the LH ICS interval; 76 of the 94 spectral estimates contained peaks in the theta range while the remainder usually contained no dominant peaks (desynchrony). An example of power spectrum estimates with and without dominant peaks is illustrated in Figure 3. An analysis of variance, using the percentage of power at each 0.5 Hz interval (from 3.5 to 17 Hz) as scores, was conducted on the spectral estimates from day 1 of self stimulation training during 2 treatments: (a) estimates during ICS interval, and (b) estimates during the 5 min. interval prior to start of self stimulation training. This analysis yielded a significant treatment by frequency interaction ($F = 7.76$, $df = 27/216$, $p < .01$). The mean percentage of power for each 0.5 Hz interval for the 2 treatments is plotted in Figure 4. The significant interaction appears to be due to (a) a decrease in percentage of power of theta peaks during ICS, and (b) an increase in frequency of the theta peaks during ICS.

The magnitude of hippocampal slow wave attenuation of some subjects during intensity test days appeared to increase as the ICS

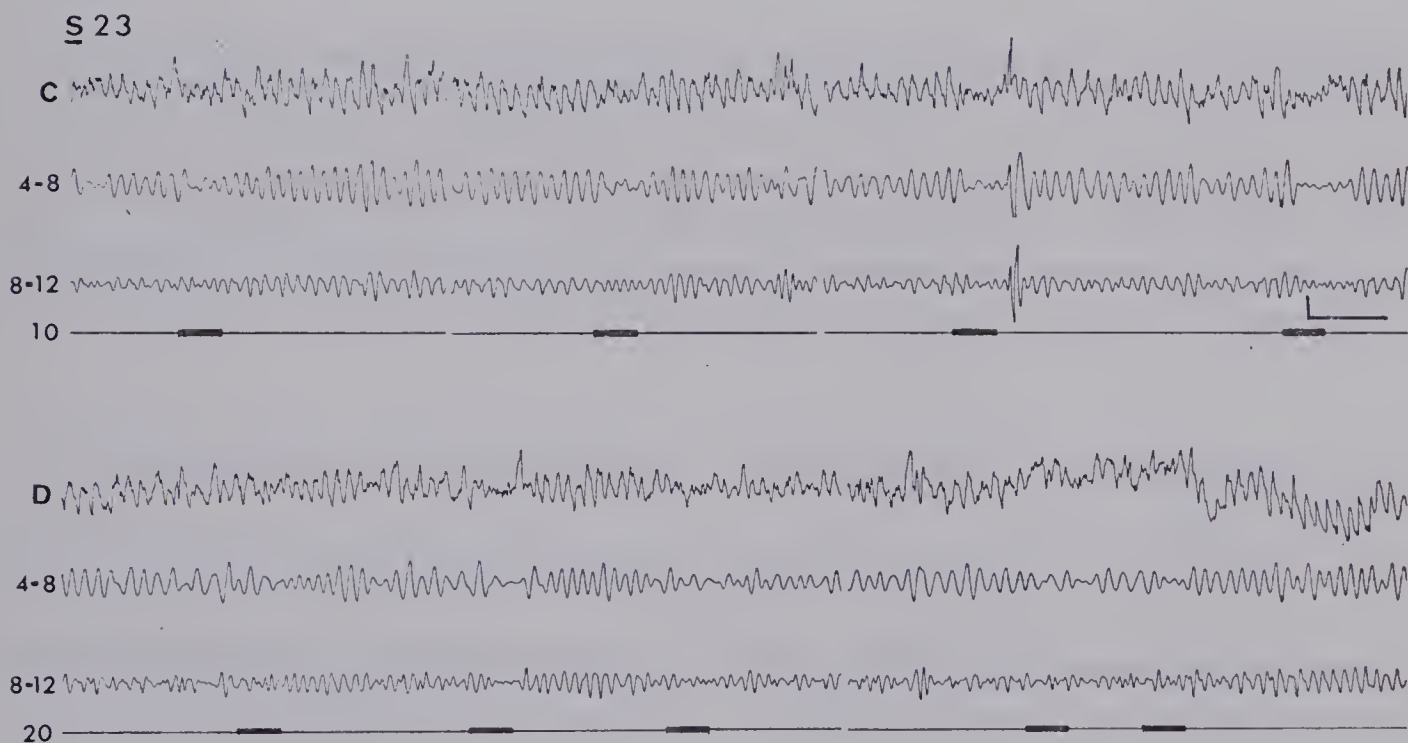
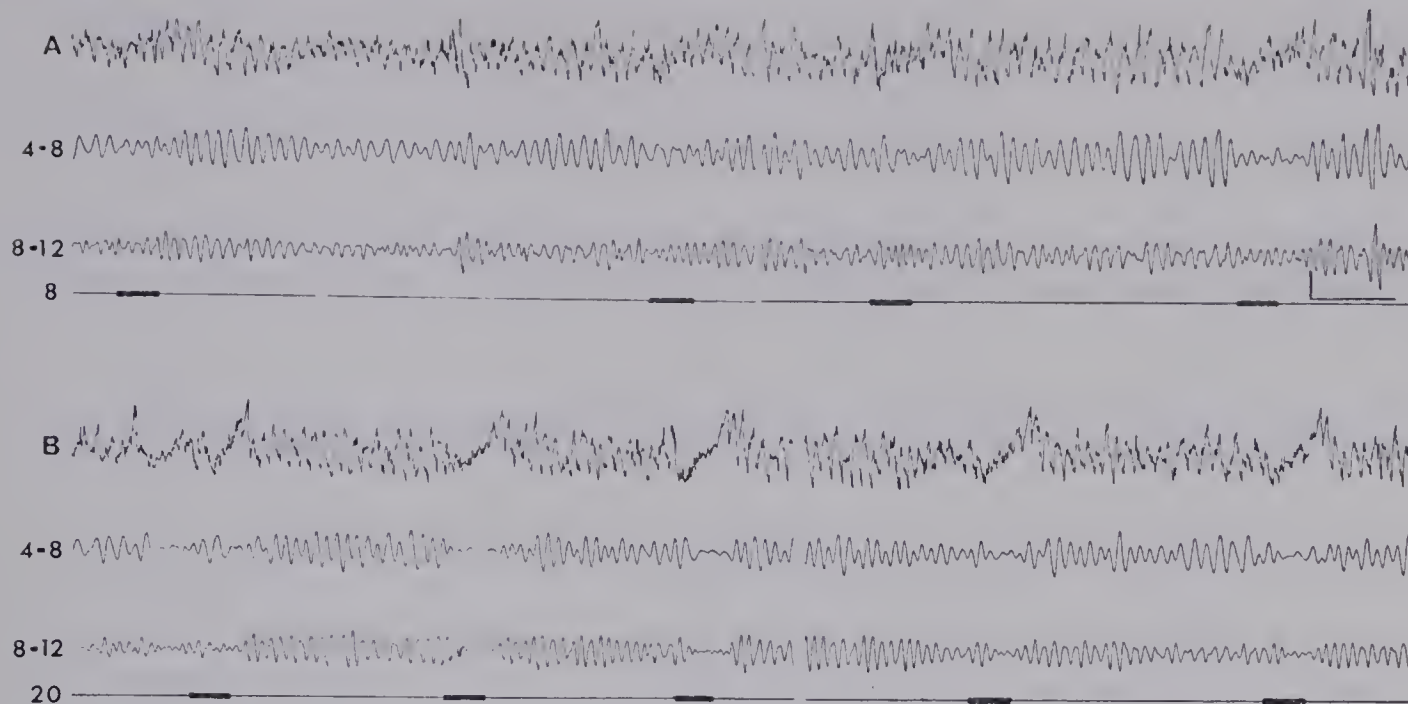


Fig. 1. Hippocampal electrical activity during 0.5 sec. trains of LH stimulation on day 1 of intensity testing. A: S 45 at 8 v. ICS. B: S 45 at 20 v. ICS. C: S 23 at 10 v. ICS. D: S 23 at 20 v. ICS. In each record, the first trace is unfiltered, the second and third traces are filtered, and the fourth trace indicates the ICS interval (solid bar). The band pass settings for the filtered traces and the ICS voltage are indicated by the values at the left. Calibration: 1 sec. and 200 μ v.

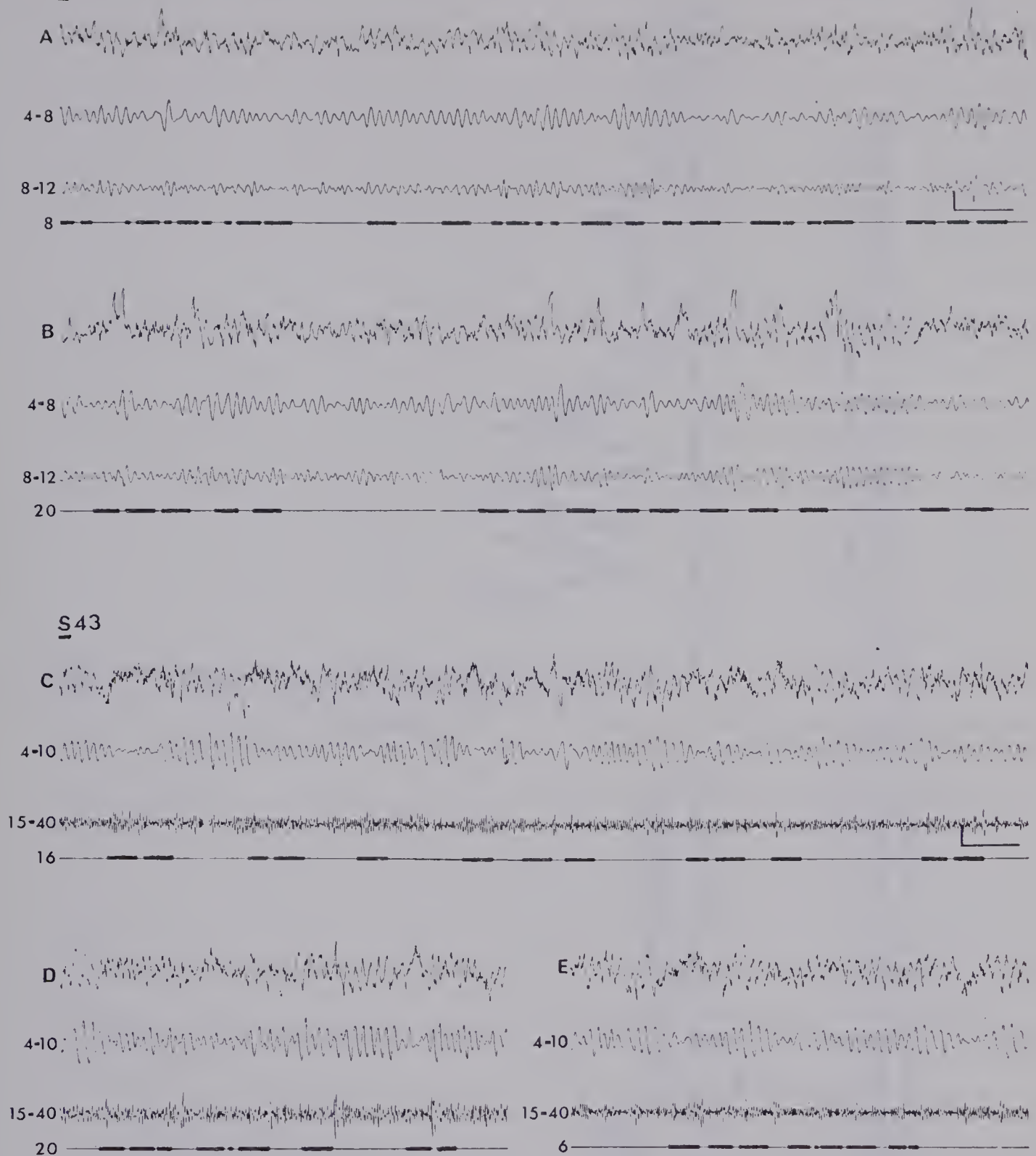


Fig. 2. Hippocampal electrical activity during day 5 of LH self stimulation training. A: S 45 at 8 v. ICS. B: S 45 at 20 v. ICS. C: S 43 at 16 v. ICS. D: S 43 at 20 v. ICS. E: S 43 at 6 v. ICS. Calibration: 1 sec. and 200 μ v.

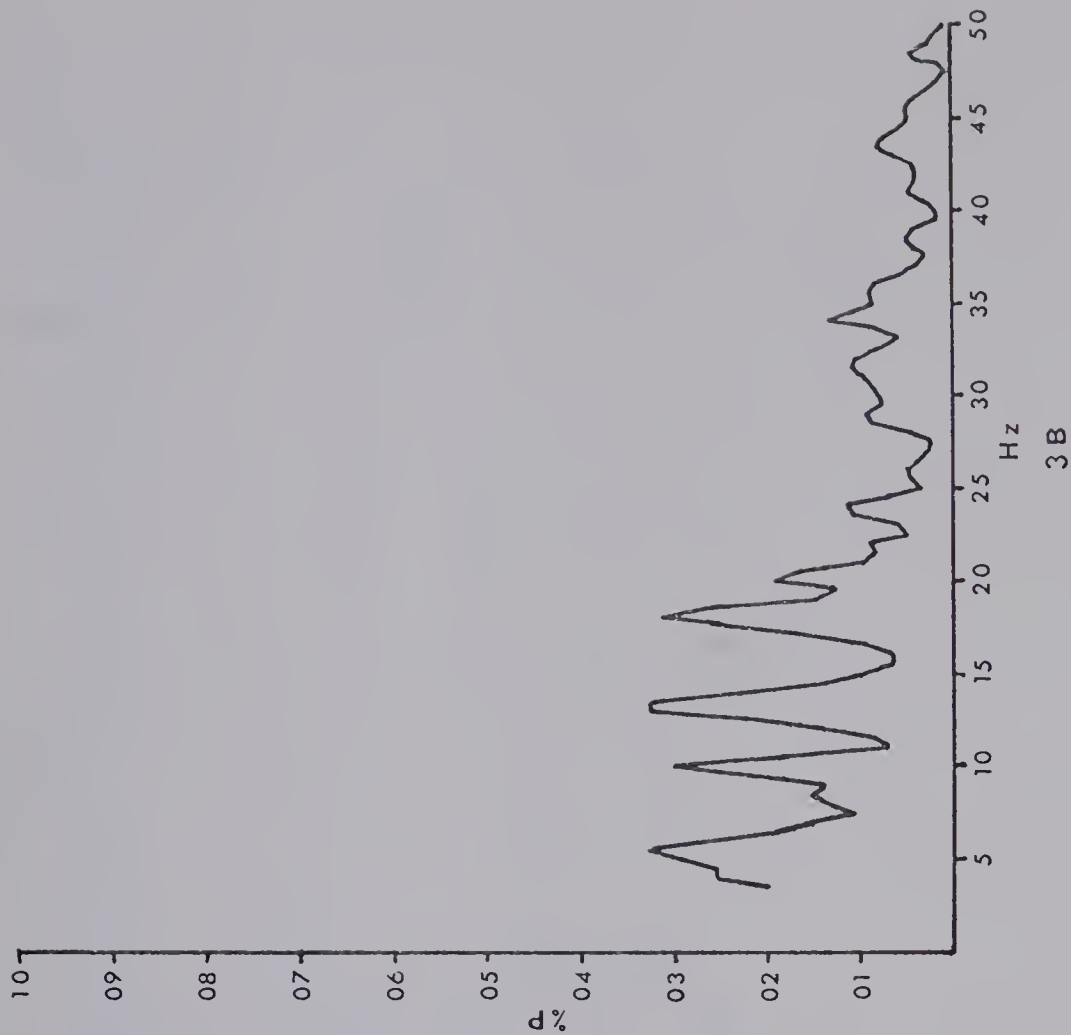
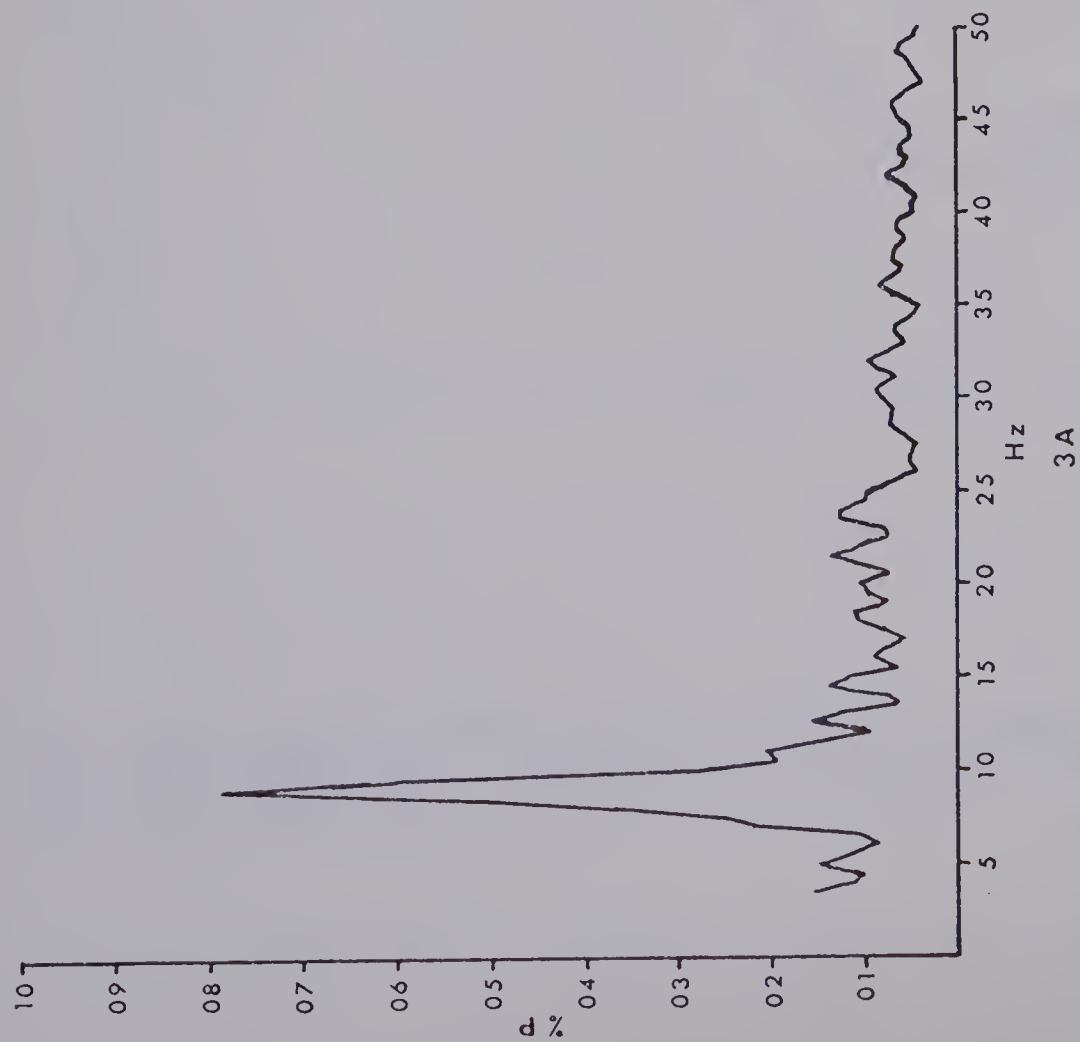


Fig. 3. Power spectrum estimates of S 22 during day 2 of LH self stimulation training. The ICS intensity and mean response rate on day 2 were 6 v. and 71R/min. respectively. A: Estimate taken at end of session. B: Estimate taken at beginning of session.

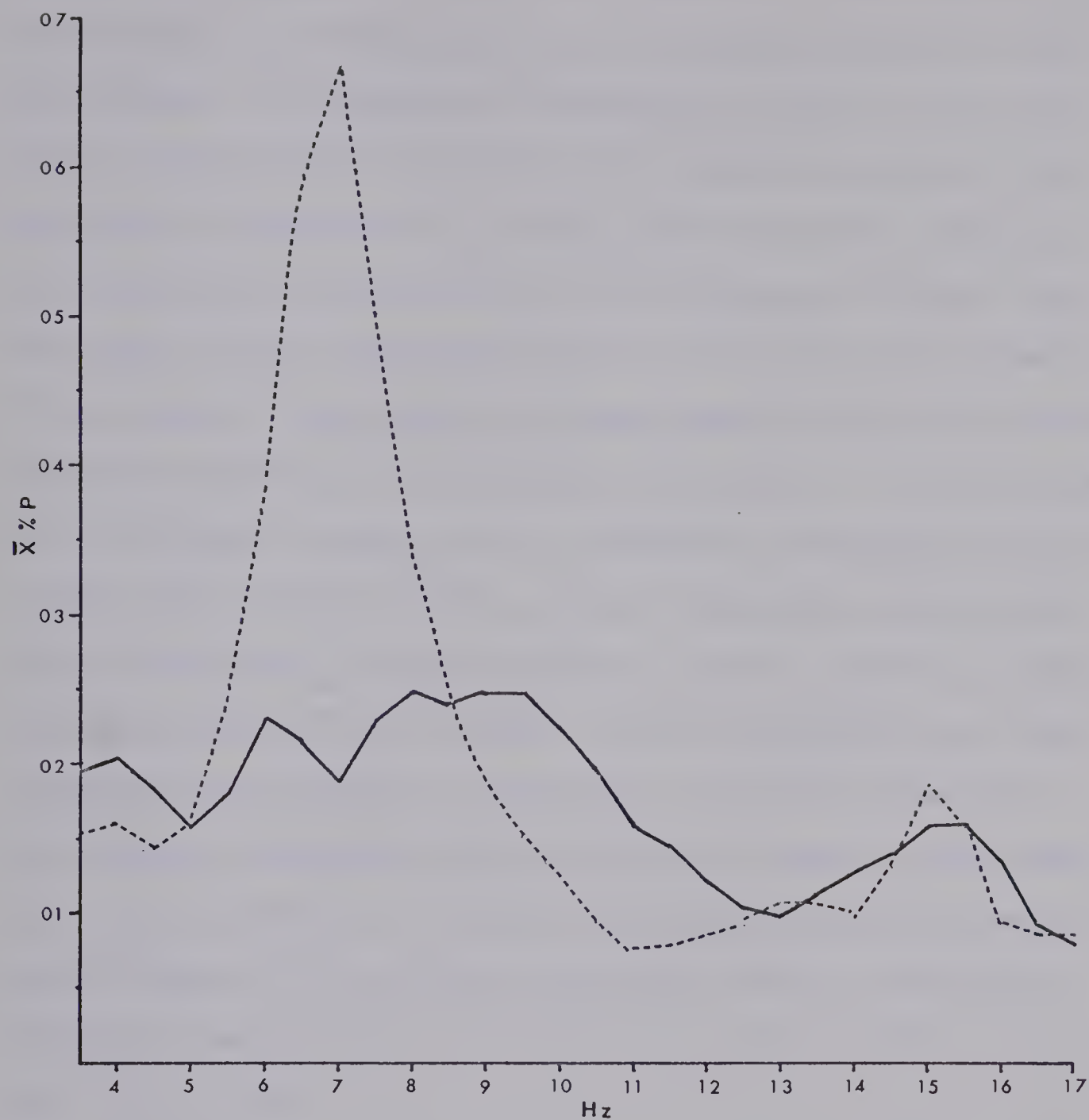


Fig. 4. Mean power spectra from day 1 of LH self stimulation training. Solid line: during ICS. Broken line: during 5 min. interval prior to start of ICS training.

intensity was increased (Figs. 1A, 1B, & 6A, 6B). This apparent relationship did not appear during self stimulation training in the same subjects. The magnitude of attenuation for \underline{S} 45 (Fig. 2A, 2B) did not differ during 8 and 20 volt self stimulation training. The magnitude of attenuation for \underline{S} 43 (Fig. 2C-E) was greater during 16 volt than during 6 volt and 20 volt self stimulation training. Nor was support for this relationship found in the correlations (between ICS v. & power of theta peak) on the power spectra containing dominant theta peaks during the self stimulation ICS interval. The observations for 4 variables, voltage of ICS (V), frequency of theta peak (H), percentage power of theta peak (P), and self stimulation response rate (R), for individual \underline{S} s were converted to Z scores, providing 76 observations for each of the 4 variables. Partial correlations were also computed on the same data to insure that a correlation between two variables was independent of the correlation of these variables with the other two variables. Both zero and second order correlations between voltage of ICS and power of theta peak were not significantly different from zero (\underline{r} VP = $-.09$, \underline{df} = 74, \underline{p} > .05; \underline{r} VP·HR = $-.07$, \underline{df} = 72, \underline{p} > .05).

The short duration stimulation during test days and self stimulation training usually also resulted in frequency shifts of theta activity. The filtered activity in Figure 1A during 8 volt ICS indicates an attenuation of 4-8 Hz activity with an increase of 8-12 Hz activity. The results of an analysis of variance, using the frequency

of theta range peaks as scores, also revealed frequency shifts. The 8 Ss with estimates available for 4 treatments (zero, low, medium, and high voltage ICS) were used; each S's spectral estimates with dominant theta range peaks were categorized into the 4 treatments and one estimate was randomly selected from each category. This analysis yielded a significant treatment effect ($F = 3.30$, $df = 3/28$, $p < .05$). A Duncan Multiple Range Test (Edwards, 1963) on the means of the 4 groups indicated that the mean spectral peak during high voltage stimulation (8.5 Hz) was significantly different ($p < .05$) from the mean spectral peaks during no stimulation (7.0 Hz) and low voltage stimulation (6.94 Hz), but did not differ significantly from the medium voltage stimulation peak (8.13)Hz). The relationship between ICS intensity and theta frequency shifts was also supported by the correlations computed on the self stimulation estimates. Significant positive zero and second order correlations were found between voltage of ICS and frequency of theta peak ($r_{VH} = +.52$, $df = 74$, $p < .01$; $r_{VH \cdot PR} = +.43$, $df = 72$, $p < .01$).

Procedural differences in delivery of ICS during intensity testing and self stimulation resulted in differences in behavior during the ICS interval. In the former, E delivered the ICS while S was grooming, resting, or exploring apparatus while in the latter, S pressed lever to deliver ICS. During threshold levels of E delivered ICS, S raised its head, pricked its ears, sniffed, and, occasionally, turned its head from side to side. At higher intensities, S froze at onset of

ICS, drew its head in slowly, then thrust it out rapidly and began sniffing and locomotor exploration behavior which lasted several seconds after termination of ICS. A wide variation in behavior within and between animals was observed during lever pressing for LH ICS. During a burst of responding, Ss were often observed rearing over the lever, pressing the lever with their forepaws. In these instances, Ss remained relatively immobile during the burst of responses, especially during the ICS interval. During other response bursts, Ss frequently shifted their position in front of the lever: depressing lever by moving head while gnawing on the lever or pressing the lever with one raised forepaw. This wide variation in behavior during lever pressing did not appear to be related to ICS intensity. The intensity of the ICS did, however, increase the self stimulation response rate. The correlations on the self stimulation estimates between intensity of self stimulation ICS and lever pressing rate were significantly different from zero ($r_{VR} = +.57$, $df = 74$, $p < .01$; $r_{VR \cdot HP} = +.49$, $df = 72$, $p < .01$).

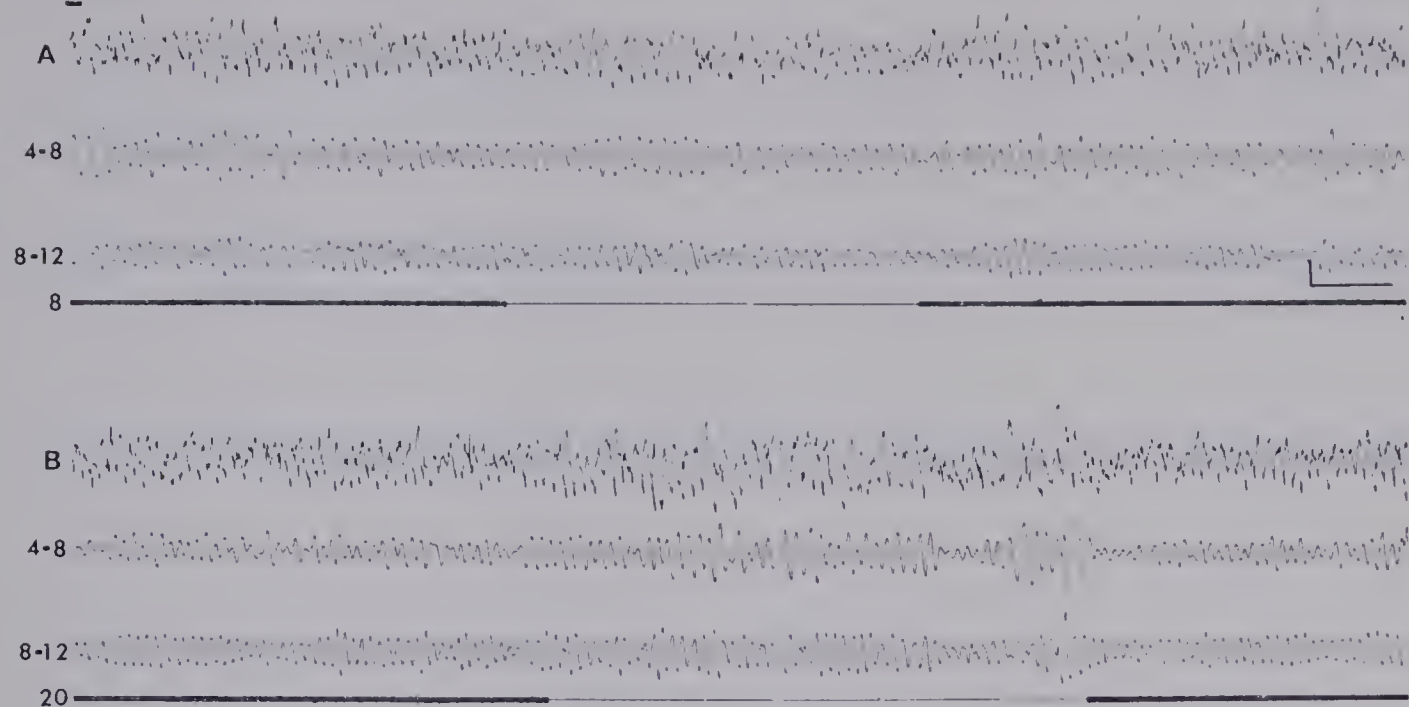
Continuous LH stimulation (over 0.5 sec. duration) during intensity test days and during escape training had similar effects on the hippocampal activity. The effects of 0.5 sec. duration LH stimulation on hippocampal activity reported above were also observed at onset of continuous stimulation. However, as LH stimulation continued, the hippocampal activity usually shifted to larger amplitude theta of a higher frequency than the theta present prior to LH stimulation. This fast

theta (7-10 Hz) during continuous stimulation usually remained for the entire duration of stimulation, with a shift to theta of a lower frequency at termination of stimulation (Figs. 5A, 5B, & 6A-D). The power spectra during LH escape training confirmed the observations of higher frequency theta during LH ICS intervals; 41 of the 51 estimates contained a dominant peak in the fast (7-10 Hz) theta range. Hippocampal activity during escape training was sampled at approximately 1-2 sec. after ICS onset, thus avoiding the frequently observed attenuation at ICS onset. An analysis of variance, using the percentage of power at each 0.5 Hz interval (from 3.5 to 17 Hz) as scores, was conducted on the spectral estimates from day 1 of escape training during 2 treatments: (a) estimates during continuous LH stimulation, and (b) estimates during the 10 sec. escape interval. This analysis yielded a significant treatment by frequency interaction ($F = 1.90$, $df = 27/216$, $p < .01$). The mean percentage of power for each 0.5 Hz interval for the 2 treatments is plotted in Figure 7. The significant interaction appears to be due to an increase in frequency of the theta peaks during ICS.

The magnitude of the theta frequency shift during continuous stimulation appeared to be correlated with the intensity of the ICS (compare 8 & 20 v. stim. for $\underline{S} 45$ in Fig. 5A, 5B, & Fig. 6A, 6B, & 10 & 20 v. stim. for $\underline{S} 23$ in Fig. 6C, 6D). The results of an analysis of variance and the correlations obtained on data from LH escape training also support this observation. The analysis of variance, using the

S 45

36.



S 46

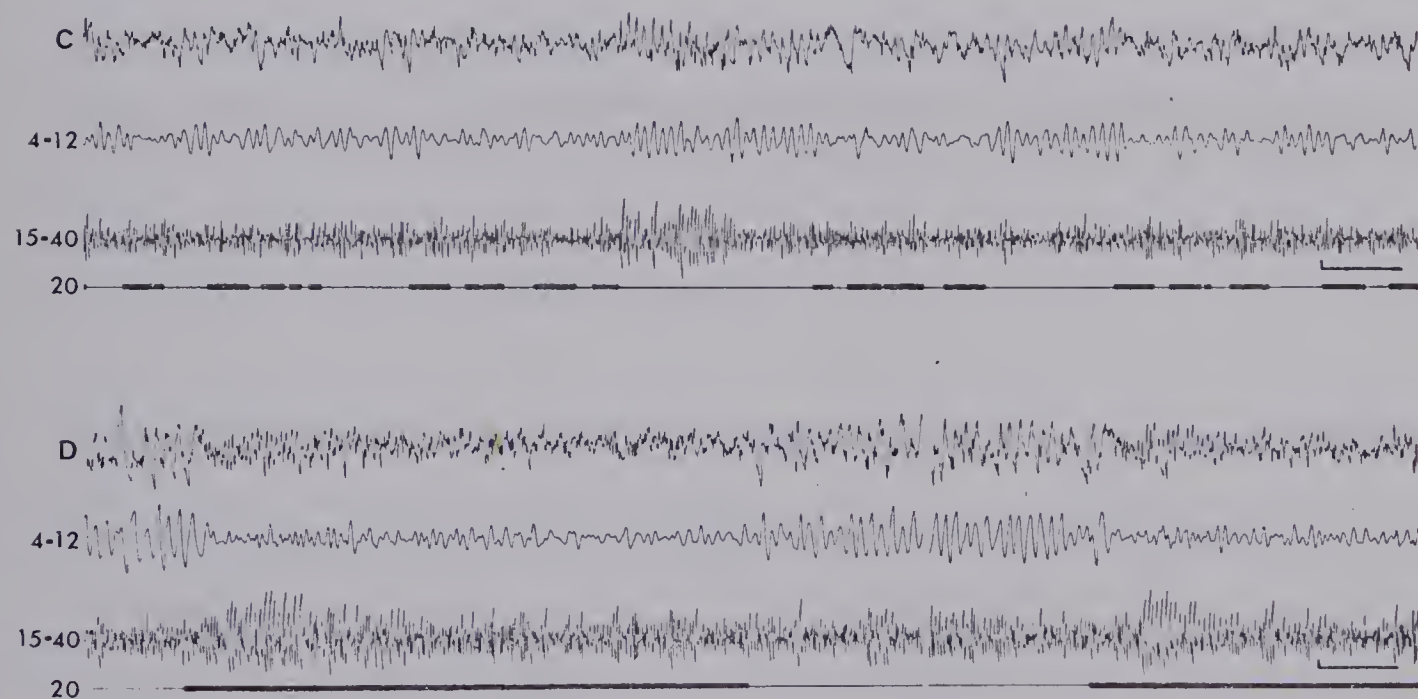
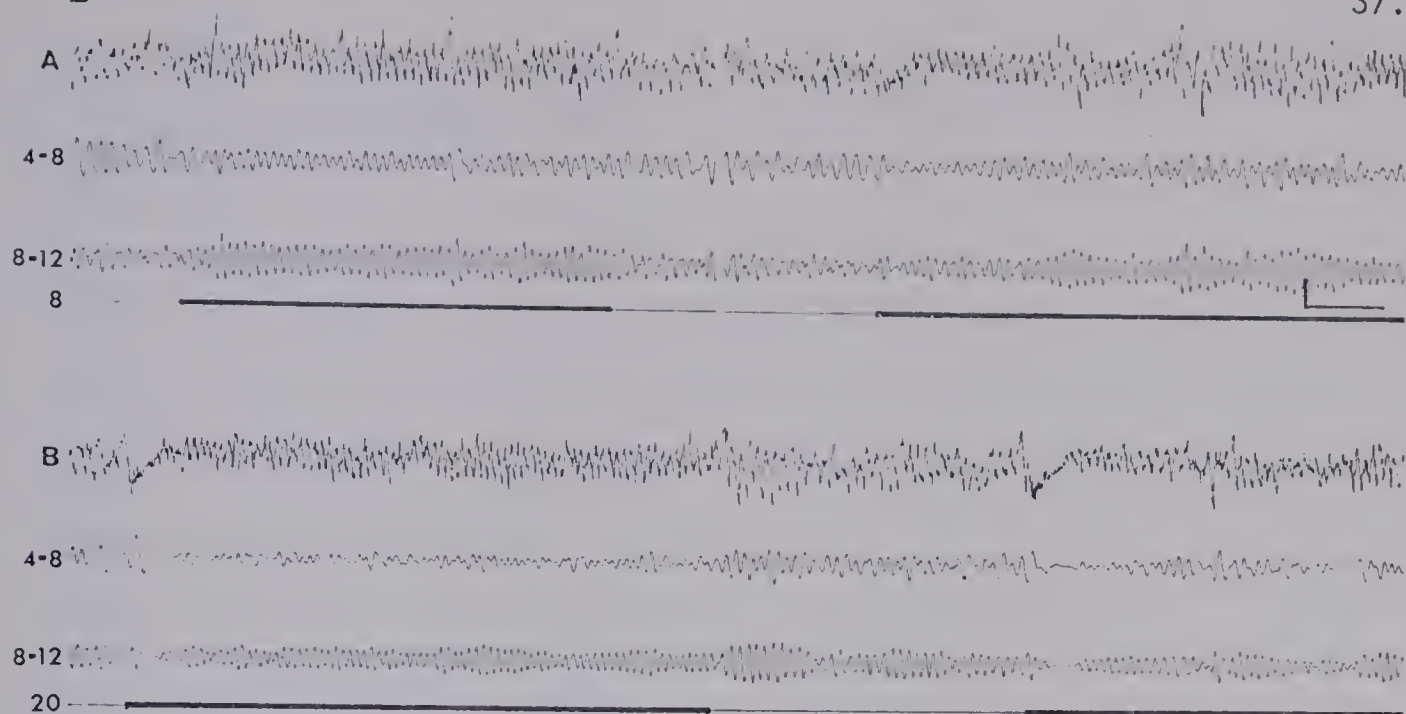


Fig. 5. Hippocampal electrical activity during LH escape and self stimulation training. A: S 45 at 8 v. ICS during day 5 of escape training. B: S 45 at 20 v. ICS during day 5 of escape training. C: S 46 at 20 v. ICS during day 4 of self stimulation training. D: S 46 at 20 v. ICS during day 4 of escape training. Calibration: 1 sec. and 200 μ v.

S 45

37.



S 23

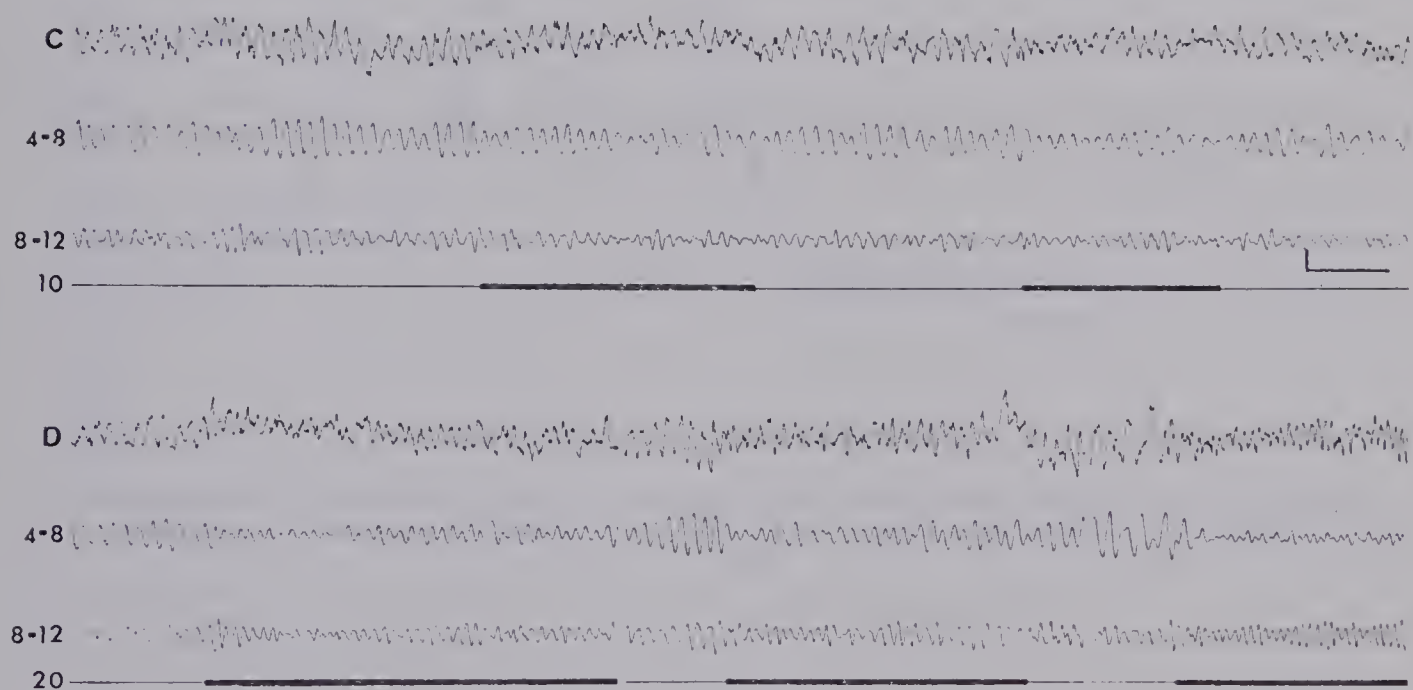


Fig. 6. Hippocampal electrical activity during long duration trains of LH stimulation on day 1 of intensity testing. A: S 45 at 8 v. ICS. B: S 45 at 20 v. ICS. C: S 23 at 10 v. ICS. D: S 23 at 20 v. ICS. Calibration: 1 sec. and 200 μ v.

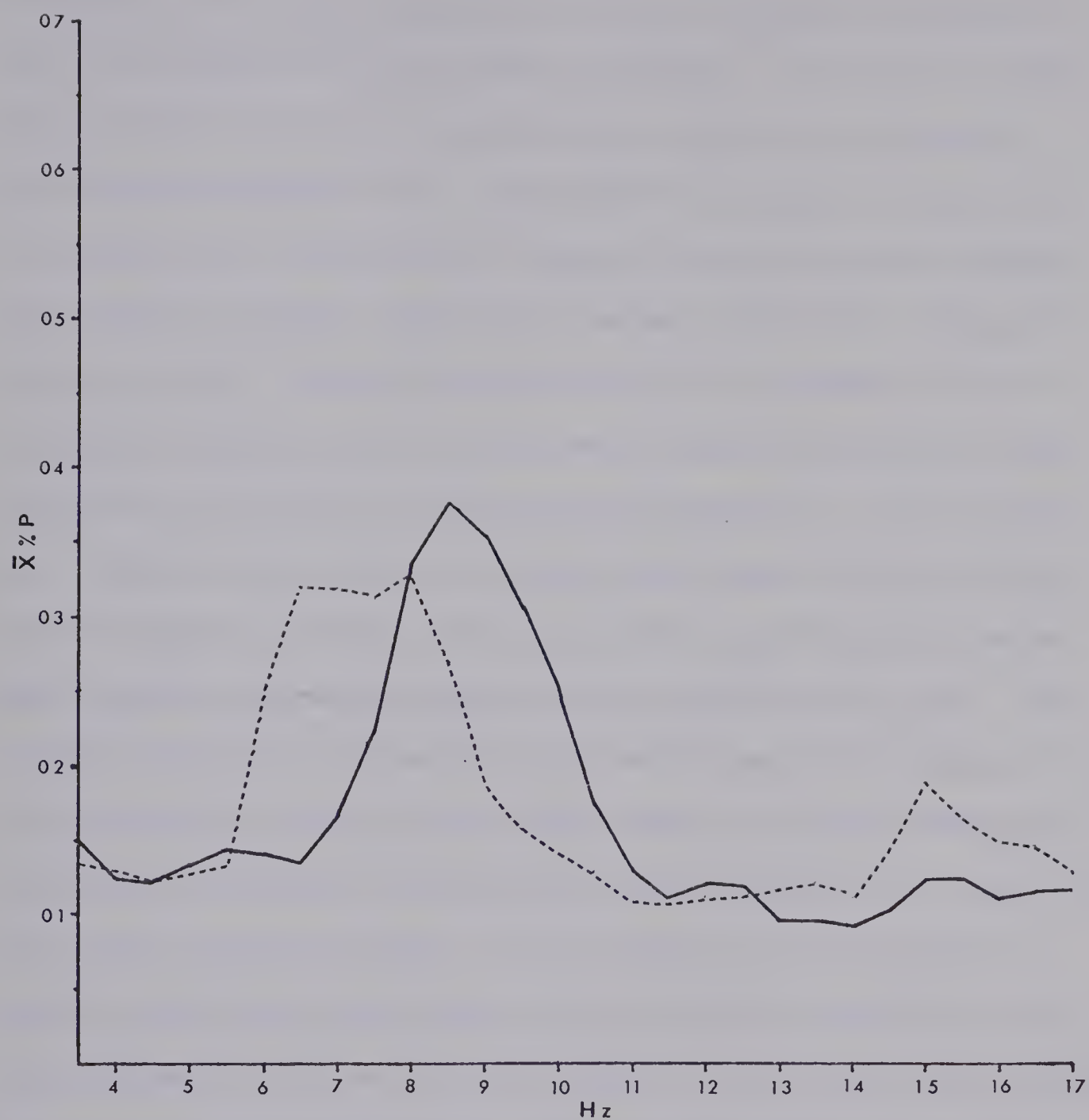


Fig. 7. Mean power spectra from day 1 of LH escape training. Solid line: during ICS. Broken line: during 10 sec. escape interval.

frequency of the theta range peak as scores, contained 4 treatments: zero, low, medium, and high voltage stimulation. The 8 Ss with estimates available for the 4 treatments were used; each S's spectral estimates with dominant theta range peaks were categorized into the 4 treatments and 1 estimate was randomly selected from each category. This analysis yielded a significant treatment effect ($F = 2.97$, $df = 3/28$, $p < .05$). A Duncan Multiple Range Test on the means of the 4 treatments indicated that the mean spectral peak during high voltage stimulation (10.25 Hz) was significantly different ($p < .05$) from the mean spectral peaks during low voltage stimulation (7.44 Hz) and the escape interval (7.81 Hz), but did not differ significantly from the mean spectral peak during medium voltage stimulation (9.19 Hz). The escape training zero and second order correlations were computed in the same manner as the zero and second order correlations during self stimulation training. The observations for 4 variables, (V), (H), (P), and escape response rate (R), for individual Ss were converted to Z scores, providing 41 observations for each of the 4 variables. The zero and second order correlations between voltage of ICS and frequency of theta peak were significantly different from zero ($r_{VH} = +.56$, $df = 39$, $p < .01$; $r_{VH \cdot PR} = +.49$, $df = 37$, $p < .01$).

The only difference in ICS elicited behavior observed during intensity test days and escape training days was the absence of a lever press during the former (E terminated ICS). Onset of stimulation during escape elicited the same behavior described during intensity testing:

raised head, pricked ears, sniffing at threshold levels and freezing and tucking of head, followed by locomotor exploration at higher intensities. Continuation of stimulation at threshold intensities elicited locomotor exploration until S either pressed the lever to escape ICS or habituated to ICS. Grooming behavior frequently followed ICS habituation. Higher intensities of ICS maintained the locomotor exploration behavior until an escape response was made. The locomotor exploration during LH stimulation differed from spontaneous locomotor exploration in that the sniffing, rhythmic head movements, and locomotion were uninterrupted during the entire ICS interval whereas spontaneous locomotor exploration was frequently interrupted as S encountered exteroceptive stimuli (i.e., S paused, raised head, and pricked ears to auditory stimuli). Increases in ICS intensity resulted in shorter S preferred ICS durations (reflected in escape response rate increase), which suggests that the ICS may have become aversive. This observation was supported by the escape training correlational data. The zero and second order correlations between voltage of ICS and escape response rate were significantly different from zero ($r_{VR} = +.51$, $df = 39$, $p < .01$; $r_{VR \cdot HP} = +.41$, $df = 37$, $p < .01$).

Although continuous LH stimulation most often elicited locomotor exploration and hippocampal theta, exceptions were observed. Figure 8 contains samples of hippocampal activity of S 22 during escape training days and intensity test days at 12 volts. The continuous stimulation during escape training (Fig. 8A, 8B) elicited freezing at onset

(and was accompanied by attenuated slow wave activity) followed by locomotor exploration (accompanied by theta waves). When continuous stimulation elicited only a pause in grooming behavior, the sniffing and head movements were accompanied by a small amount of theta (Fig. 8C). When continuous stimulation did not interrupt grooming behavior, hippocampal activity consisted of large amplitude, slow, irregular waves (Fig. 8D).

Stimulation of the LH during self stimulation and escape training of S 46 elicited behavior indistinguishable from the other Ss' behavior but the accompanying hippocampal activity contained frequent bursts of fast wave (15-40 Hz) activity rather than theta activity (Fig. 5D). Lateral hypothalamic stimulation elicited locomotor exploration (always accompanied by theta waves in other Ss) which was accompanied by an attenuation of slow wave activity, with frequent bursts of fast wave activity in S 46. These observations were confirmed in this S's power spectra, only 5 of the 13 estimates during self stimulation and 2 of the 7 estimates during escape training contained a dominant peak in the theta range (Fig. 9A). The other spectra of this subject contained either no dominant peaks or a dominant peak in the fast wave range (Fig. 9B).

A comparison of self stimulation response rates between group I (received self stimulation first and escape training second) and group II (received training in reverse order) revealed an order effect. Subjects in group II self stimulated at threshold levels of ICS intensity

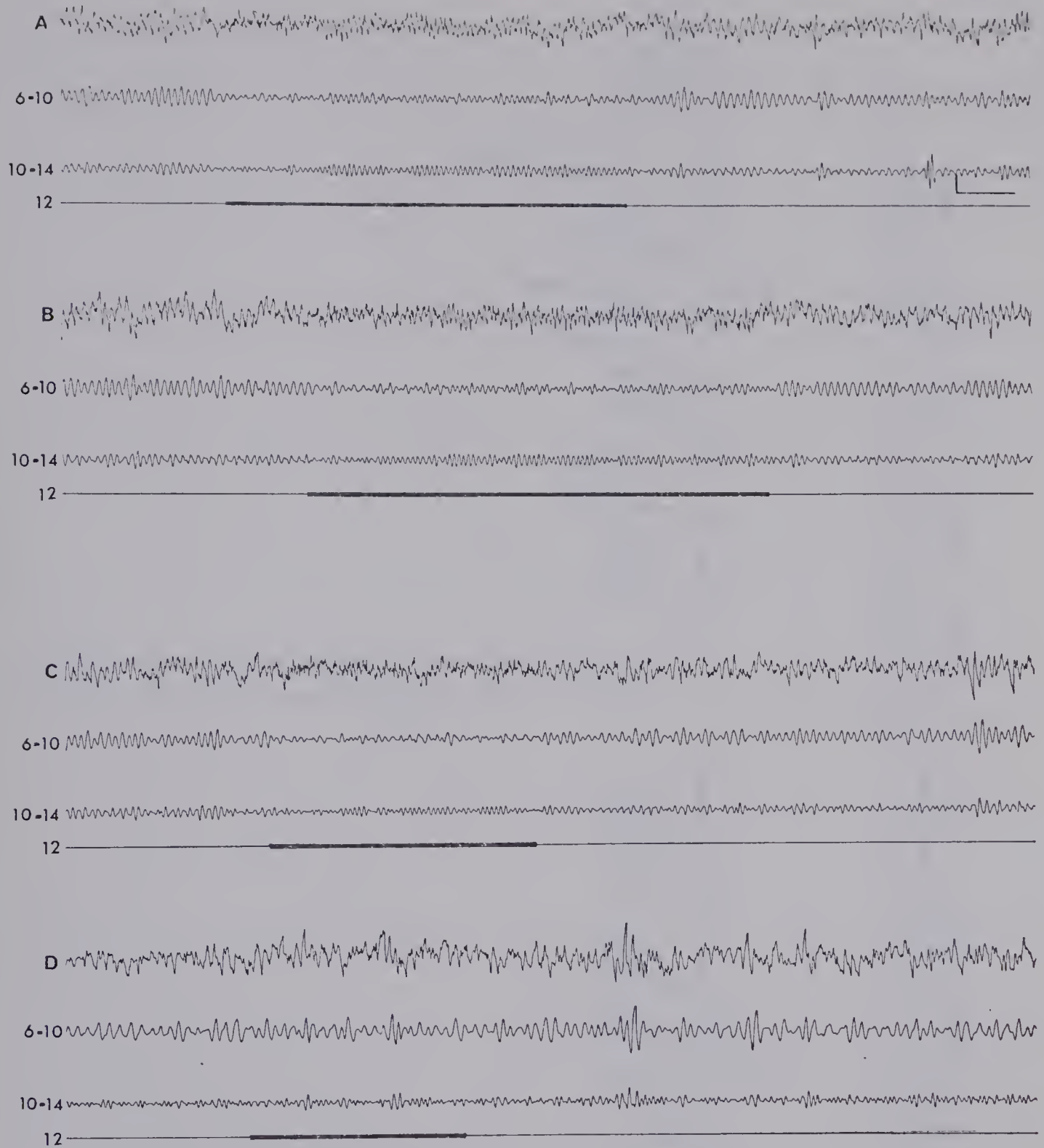


Fig. 8. Hippocampal electrical activity of S 22 during LH escape training and during intensity test days at 12 v. A: day 1 of escape training. B: day 5 of escape training. C: day 2 of intensity testing. D: day 3 of intensity testing. Calibration: 1 sec. and 200 μ v.

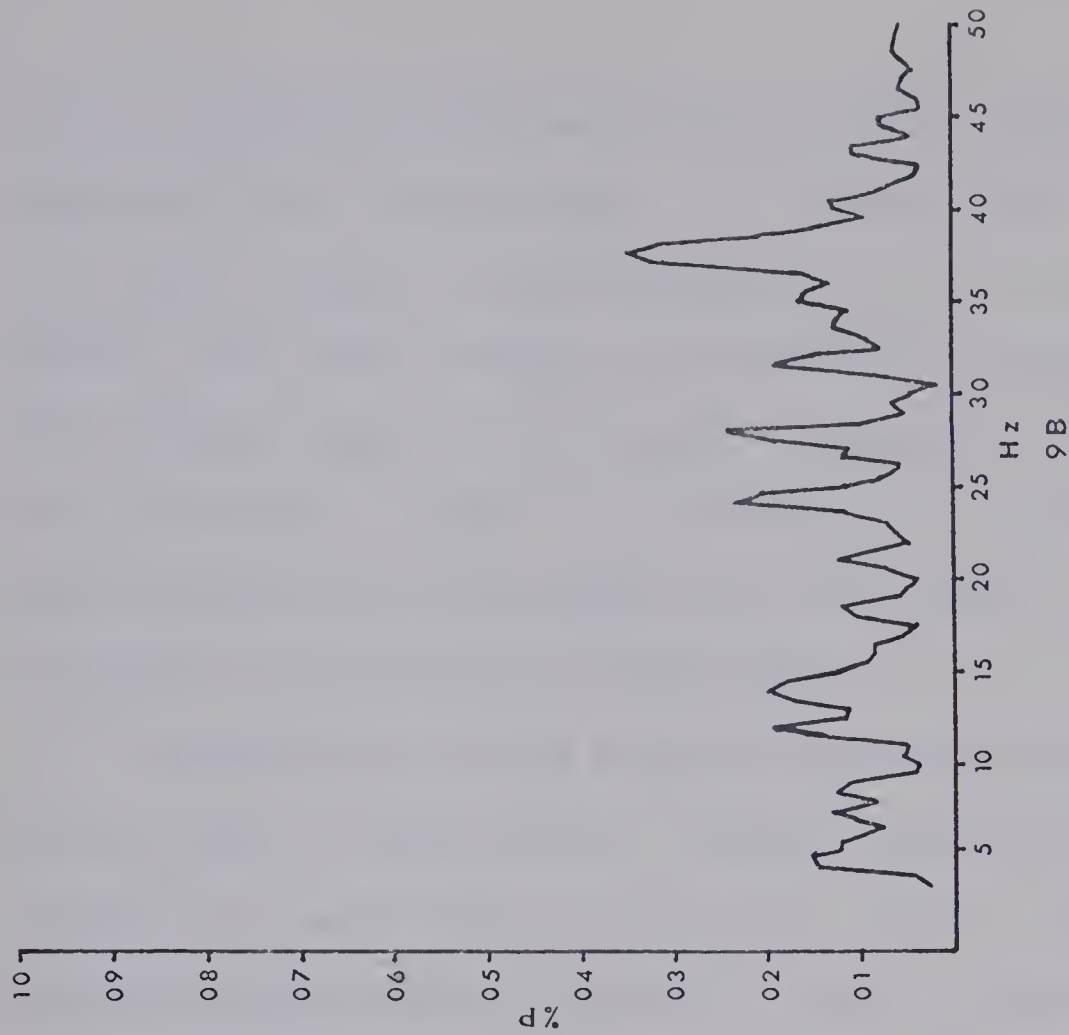
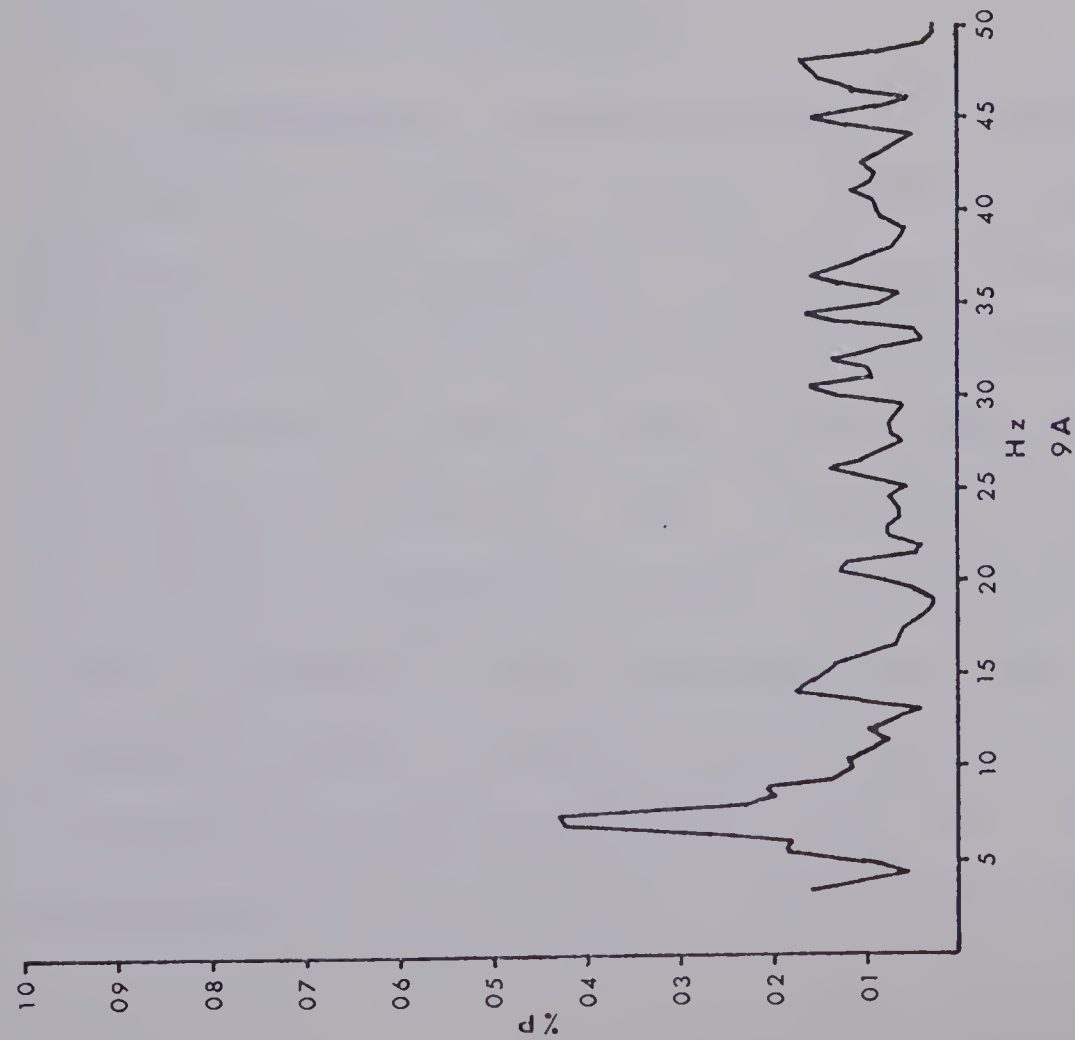


Fig. 9. Power spectrum estimates of S 46 during LH self stimulation training. A: Estimate from day 4 of training. The ICS intensity and mean response rate were 3 v. and 6.4R/min. respectively. B: Estimate from day 5 of training. The ICS intensity and mean response rate were 16 v. and 7.9R/min. respectively.

but the response rate was low and often failed to continue for the duration of the training session. An increase in ICS intensity (1 1/2 to 2 times threshold v.) was necessary for 3 of the 4 Ss in group II. However, even after increases in ICS intensity, the mean stimulation rates between groups I and II were not comparable. The mean response rates for group I on days 1, 2, and 3 were 60, 67, and 73R/min. respectively while the mean response rates for group II on days 1, 2, and 3 were 32, 43, and 52 R/min. respectively.

A comparison of escape response rates between groups I and II did not reveal an order effect. The mean response rates for group I on days 1, 2, and 3 were 1.32, 1.45, and 1.66R/min. respectively while the mean response rates for group II on days 1, 2, and 3 were 1.27, 1.32, and 2.16R/min. respectively.

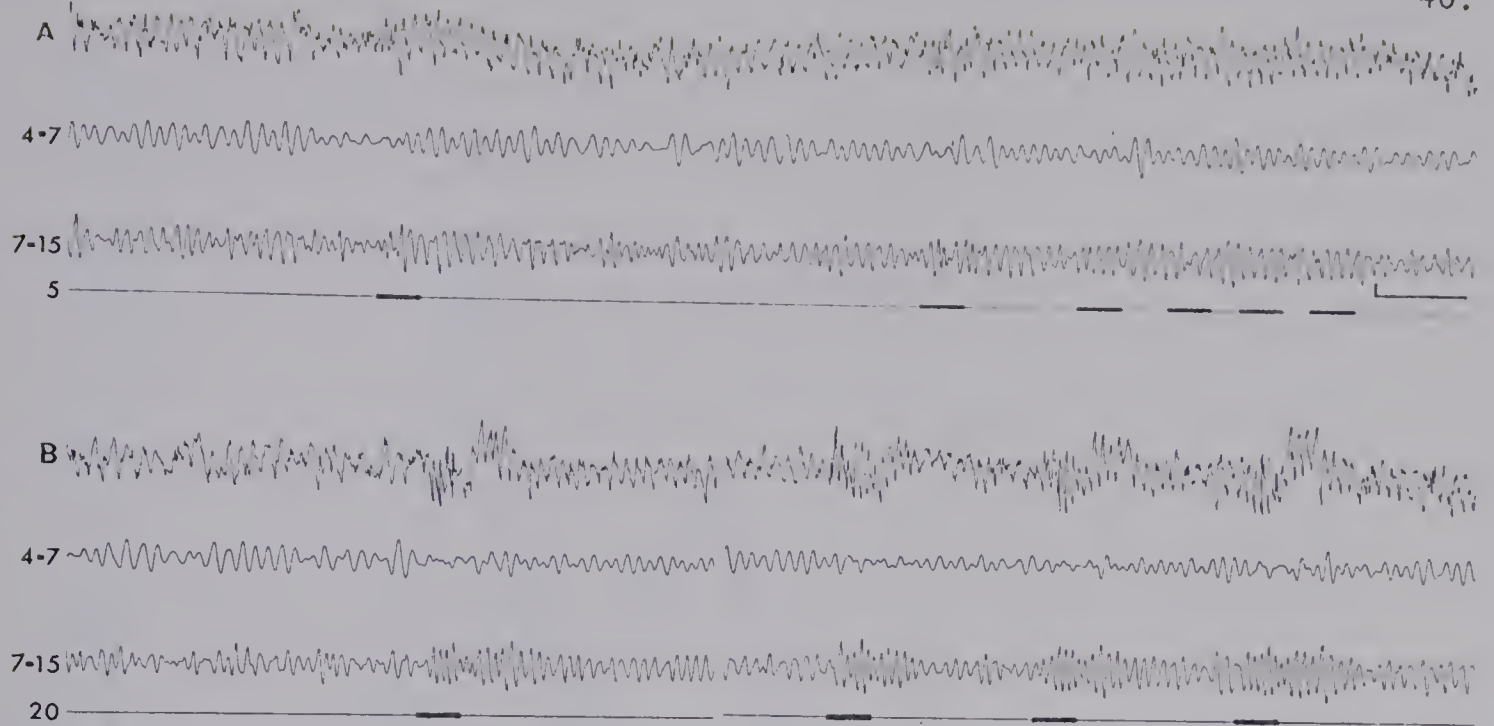
DT stimulation. No differences were found between contralateral, ipsilateral, and bilateral DT placement effects on hippocampal activity, therefore, the three placements will be discussed together. Stimulation of the DT at or above behavioral threshold reliably shifted ongoing hippocampal activity to theta activity which continued into the post-stimulatory period (Fig. 10A). Increases in DT stimulation intensity elicited corresponding increases in behavioral activity and increases in frequency of the accompanying theta rhythm. The highest frequency of theta (9-14 Hz) was observed during ICS intensities eliciting bursts of running and/or jumping (Fig. 10B). The same DT ICS intensity which initially elicited violent running and/or jumping

(accompanied by fast theta) later in training elicited well controlled escape behavior and was accompanied by theta of a lower frequency. Unlike LH stimulation onset, attenuation of slow wave activity at DT stimulation onset was never observed at any ICS intensity level during intensity test days or DT escape training.

Recurrent trains of DT stimulation during DT escape training, at or slightly above threshold levels, were accompanied by theta waves throughout the training period, with occasional desynchronous periods appearing during the 10 and 20 second escape intervals (Fig. 10C, 10D). The presence of theta activity during the DT ICS trains as well as during most of the escape intervals was confirmed by the analysis of variance on the power spectra gathered during 6 of the 14 DT training days. The analysis of variance, using the percentage of power at each 0.5 Hz interval (from 3.5 to 17 Hz) as scores, contained 3 treatments: (a) estimates during the 0.5 sec. ICS interval, (b) estimates during the 0.5 sec. post-stimulatory interval, and (c) estimates during the 10 and 20 sec. escape intervals. This analysis of variance yielded a significant treatment by frequency interaction ($F = 12.94$, $df = 54/378$, $p < .005$). The mean percentage of power at each 0.5 Hz interval for the 3 treatments is plotted in Figure 11. The significant interaction appears to be due primarily to increases in theta frequency over treatments: (a) 7.5 Hz during the escape interval, (b) 8.0 Hz during the 0.5 sec. post-stimulatory interval, and (c) 10.0 Hz during the 0.5 sec. ICS interval.

S 37

46.



S 39

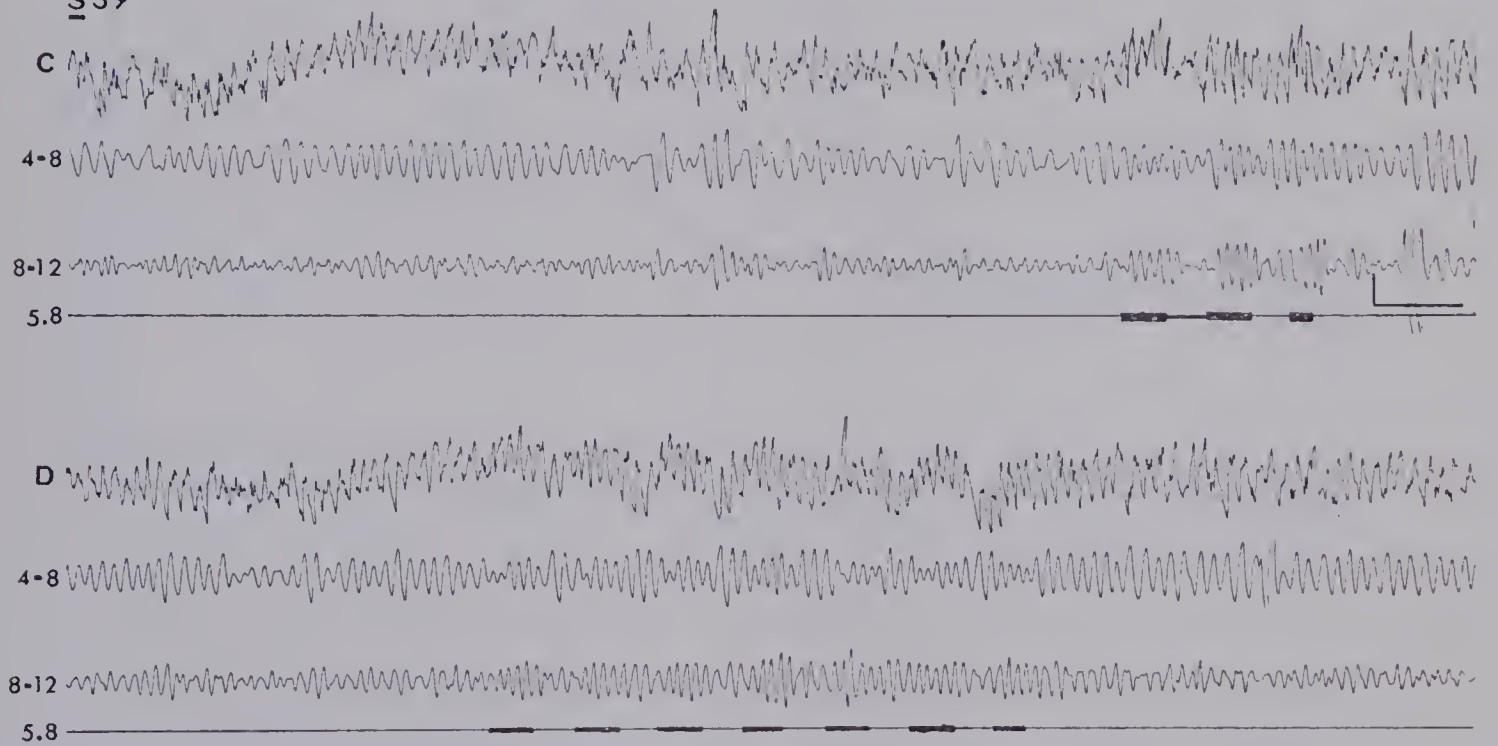


Fig. 10. Hippocampal electrical activity during DT intensity testing and escape training. A: S 37 at 5 v. ICS on day 2 of intensity testing. B: S 37 at 20 v. ICS on day 2 of intensity testing. C: S 39 at 5.8 v. ICS from beginning of day 14 escape training session. D: S 39 at 5.8 v. ICS from end of day 14 escape training session. Calibration: 1 sec. and 200 μ v.

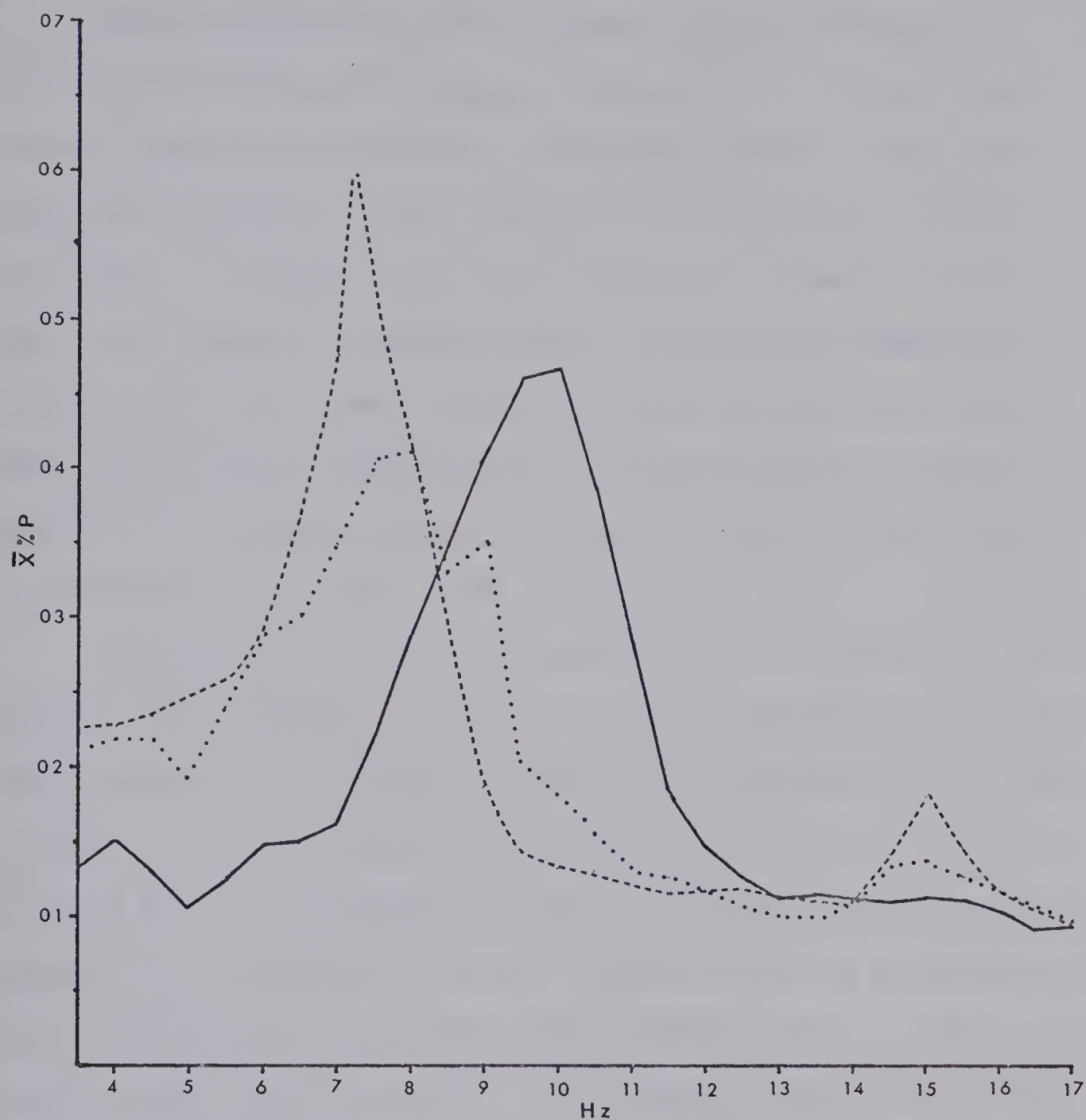


Fig. 11. Mean power spectra from DT Ss. Solid line: during 0.5 sec. ICS interval. Dotted line: during 0.5 sec. post-stimulatory interval. Broken line: during 10 and 20 sec. escape intervals.

Visual inspection of theta amplitude occurring between ICS intervals and during ICS intervals at high and low ICS intensities during intensity test and escape training days did not reveal any systematic increases in theta amplitude as the frequency of theta increased. To further test for any relationship between theta frequency and amplitude, a product moment correlation was computed on the 133 (out of 144) power spectra containing a dominant theta range peak. This product moment correlation between frequency of spectra peak (H) and percentage power of that peak (P) was not significantly different from zero ($r_{HP} = +.05$, $df = 131$, $p > .05$).

The behavior of DT Ss, at threshold levels of stimulation, was similar to the behavior of LH Ss at threshold stimulation: S raised head, pricked ears, sniffed, and occasionally, turned head from side to side. As DT ICS intensity was increased, similarities to LH ICS elicited behavior disappeared. Instead of elicited locomotor exploration, DT Ss crouched; with further increases producing contraversive turning (bilateral DT Ss turned either direction) until a burst of running and/or jumping occurred. The threshold intensities remained relatively stable after 14 days of recurrent DT stimulation. The intensities first producing jumping, however, increased over training days. This factor necessitated slight increases in ICS intensities within and between training days to maintain escape response rates. The behavior of DT Ss during training consisted of a burst of running, initiated during the ICS interval and terminated during the post-

stimulatory interval with normal locomotor exploration or grooming activity observed during the escape interval.

Histological results. Representative samples of hippocampal electrode placements are shown in Figure 12 (these placements are for the subjects whose data are shown in Figs. 1, 2, 5, 6, 8, & 10). All Ss with hippocampal placements comparable to examples A through E contained mostly synchronous theta or irregular, slow wave activity. The Ss with placements comparable to example F contained either theta and slow, irregular activity or theta and slow, irregular activity mixed with fast wave activity. Of these gyrus dentate placements, no apparent anatomical relationship was found between "good theta placements" (little fast activity) and "poor theta placements" (fast wave activity mixed with theta activity). The gyrus dentate placement with electrode tips positioned across the granule cells (example G) was the exception which contained some dominant fast wave peaks during LH stimulation.

The approximate location of the electrode tips for all LH Ss are shown in Figure 13. No apparent relation appeared between LH tip location and the effects on behavior or hippocampal activity.

The approximate location of the electrode tips for all DT Ss are shown in Figure 14. The only observed relationship between behavior and electrode placement was the lack of contraversive turning in the 2 Ss with bilateral placements.

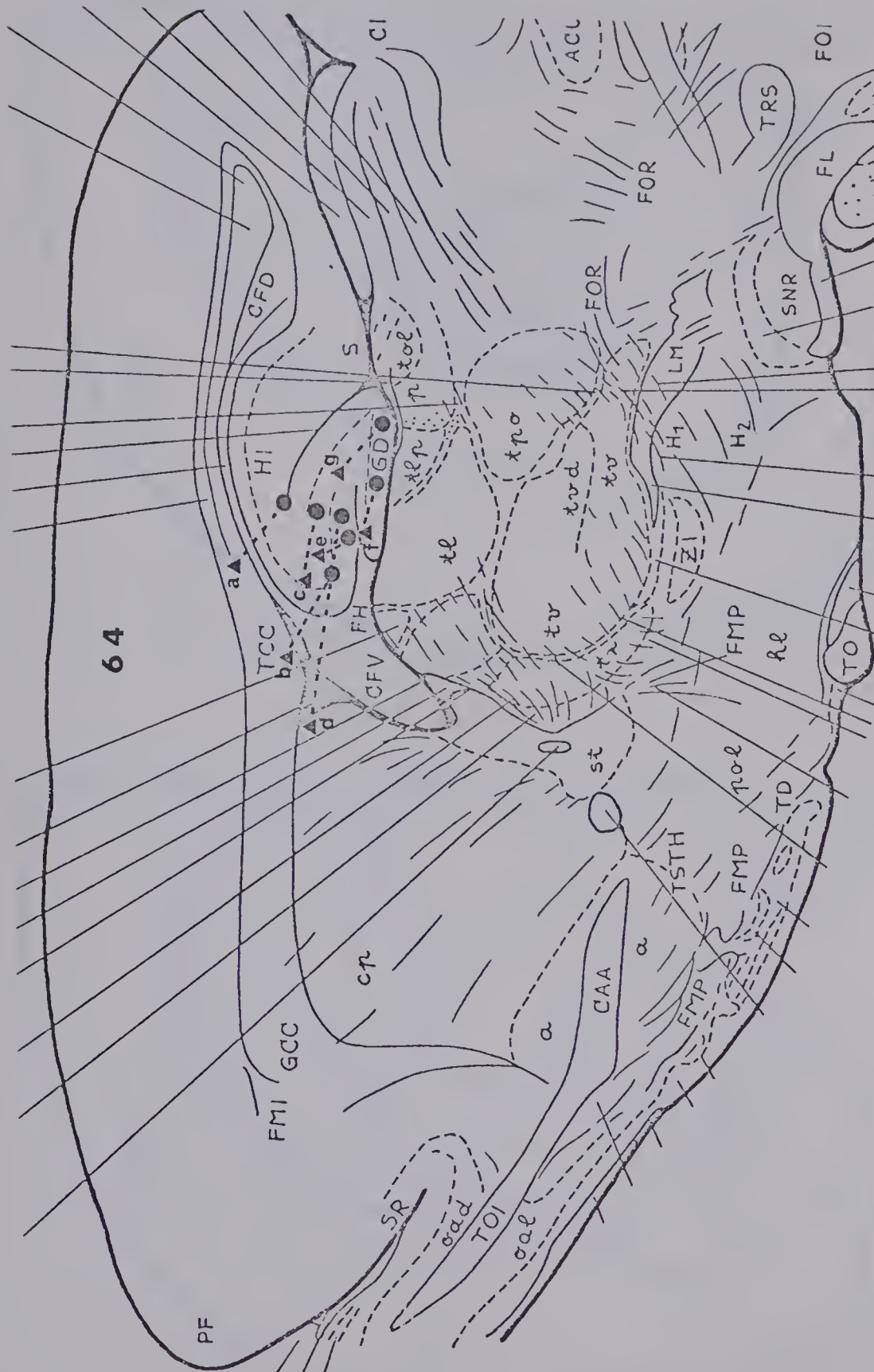


Fig. 12. Approximate locations of 7 hippocampal electrode placements projected on plate 64 from the König and Klippel atlas (1963). A: S 37. B: S 22. C: S 39. D: S 43. E: S 23. F: S 45. G: S 46. The triangles denote the anterior tip of the electrodes which were located approximately 0.5 mm. medial to plate illustrated. The circles denote the posterior tip of the electrodes which were located approximately 0.5 mm. lateral to plate illustrated. All hippocampal electrodes were located in the left hemisphere.



Fig. 13. The approximate location of the LH electrode placements (König & Klippel, 1963). The circles denote loci located on plates illustrated (40 & 43). The triangles denote loci anterior to plates illustrated (plates 39 & 42). The squares denote loci posterior to plates illustrated (plates 41 & 44). For reasons of clarity, the placements, located in the right hemisphere, are illustrated in left hemisphere (posterior view).

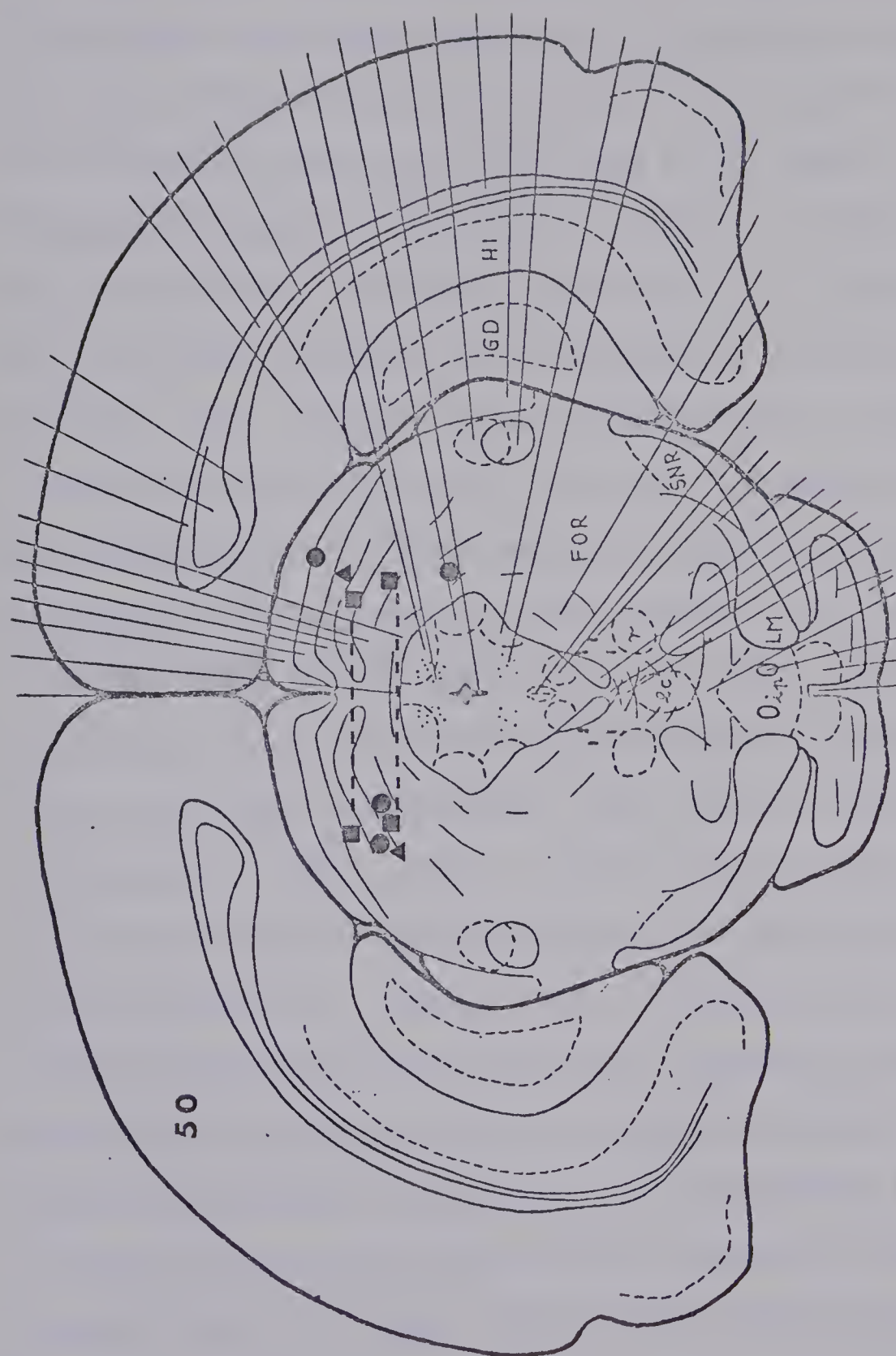


Fig. 14. The approximate locations of the DT electrode placements. The circles were located on plate illustrated (König & Klippel, 1963, plate 50). The triangles denote loci located on anterior plate (49). The squares denote loci located on posterior plate (52). The 2 bilateral placements are represented by dotted lines. Implants on the right or left side of the brain are shown on the corresponding side of the figure (posterior view).

Discussion

The results of the present study do not support the relationships between hippocampal electrical activity and the rewarding-punishing characteristics of brain stimulation suggested by either Grastyán and his associates (1965, 1966) or Ito (1966). First, the hippocampal response to rewarding LH stimulation, within subjects, was not invariant. For example, continuous 12 v. stimulation evoked the following at different times in the same S: theta activity; large amplitude, slow, irregular activity (desynchrony); or attenuated irregular activity (desynchrony) (Fig. 8). The onset of LH ICS in most Ss frequently elicited attenuated irregular activity or attenuated theta activity followed by large amplitude, fast theta activity (7-10 Hz) if the ICS remained on (Figs. 5B, 6B-D). The presence of theta activity during LH stimulation confirms the results of several researchers (Kramis & Routtenberg, 1969; Paxinos & Bindra, 1970; Pond & Schwartzbaum, 1970). Second, aversive (DT) ICS evoked a pattern of fast theta activity (7-10 Hz) similar to that observed during continuous LH stimulation. Although theta or desynchrony has been reported with LH stimulation, aversive ICS (dorsal tegmentum, periaqueductal grey mid brain region, and medial hypothalamus) appears to elicit only theta activity (Pond & Schwartzbaum, 1970; Routtenberg & Kramis, 1968) or theta mixed with fast wave activity at higher ICS intensities (Stumpf, 1965; Torii, 1961). Only Grastyán and his associates reported desynchrony with medial hypothalamic stimulation (Grastyán, Karmos,

Vereczkey, Martin, & Kellenyi, 1965; Grastyán, Karmos, Vereczkey, & Kellenyi, 1966). In addition, the results of rewarding septal stimulation also fail to confirm the above hypotheses (Ball & Gray, 1971; Ito, 1966; Pond & Schwartzbaum, 1970).

Grastyán and his associates also reported that behavioral and hippocampal rebound activity always occurred upon termination of either rewarding or punishing ICS (Grastyán, Karmos, Vereczkey, Martin, & Kellenyi, 1965; Grastyán, Karmos, Vereczkey, & Kellenyi, 1966). The present study and others (Kramis & Routtenberg, 1969; Pond & Schwartzbaum, 1970; Routtenberg & Kramis, 1968) have not confirmed this rebound phenomenon since stimulation which evoked theta activity never produced a desynchronous rebound at offset.

The results of the present study suggest that the discrepant hippocampal activity during LH stimulation in the studies by Grastyán et al. (1965, 1966) and Ito (1966) can be accounted for in terms of the procedural differences used by these researchers in stimulating the LH. Continuous LH stimulation during escape training (Grastyán's procedure) most often elicited large amplitude theta activity, confirming Grastyán's results. Short duration (0.5 sec.) LH stimulation during self stimulation training (Ito's procedure) seldom elicited large amplitude theta activity; instead, attenuated activity was most often observed. This attenuated activity looked (visual inspection) very much like desynchronous activity, which confirms, in part, the results of Ito. It was noted in the present study that continuous

LH ICS onset usually elicited attenuated activity for approximately 1/2 to 3/4 of a second, followed by large amplitude theta activity. Although Grastyán et al. (1965, 1966) did not mention the presence of attenuated hippocampal activity elicited by ICS onset, inspection of their published hippocampal activity records during LH (and other sites) stimulation revealed the presence of a short burst of attenuated activity following ICS onset prior to the occurrence of theta activity. This finding suggests that Ito would have also found theta activity during LH stimulation if his ICS duration had been longer.

Although the procedural differences in the present study accounted for the different hippocampal activity reported above, these differences cannot account for the type of hippocampal desynchronous activity reported by Ito (1966). Power spectra analysis of the attenuated activity (which looked desynchronous) during short duration LH ICS revealed that the attenuated activity usually consisted of small amplitude theta activity rather than small amplitude, fast wave (15-40 Hz) activity (desynchrony). Ito, on the other hand, reported fast wave activity during LH self stimulation, a result present in only one S in the present study. This subject's hippocampal activity during continuous and self stimulation occasionally contained 20-40 Hz activity. The most plausible explanation for this occasional fast wave activity is in terms of the hippocampal electrode placement. According to Vanderwolf (1969a), theta activity and large amplitude, slow, irregular waves during voluntary movement are most clearly recorded from CA1,

CA2, and CA3 areas of the dorsal hippocampal pyramids. The subiculum and CA4-gyrus dentate areas yield mostly 15-50 Hz activity or some mixture of fast wave and slow wave activity. The electrode tips of the hippocampal placement in this subject were located across the granule cells of the gyrus dentate. It is impossible to determine whether the fast wave activity reported by Ito was due to electrode placement since he did not specify the exact hippocampal location.

The desynchronous activity, or attenuation of theta amplitude often observed during self stimulation, and occasionally, during continuous stimulation was not observed by other researchers who used comparable stimulation procedures. Kramis and Routtenberg (1969), using ipsilateral recording electrodes, and Pond and Schwartzbaum (1970), using bilateral recording electrodes, reported hippocampal theta activity during both continuous stimulation and self stimulation of the LH. The amplitude of the theta during the self stimulation ICS was greater than the amplitude of the theta prior to or following the ICS interval. It is impossible to rule out differences in hippocampal electrode placements as an explanation of the discrepant findings since the orientation of the electrode tips with respect to one another in the present study differed considerably from that in the studies by Kramis and Routtenberg and Pond and Schwartzbaum. However, the present study found desynchrony and attenuated theta activity during LH stimulation from electrodes optimally placed in or near the apical dendritic layer of the CA1, CA2, and CA3 cells and from electrodes less

optimally placed, making it unlikely that the discrepant findings are simply due to differences in hippocampal electrode placements.

Evidence for the attenuation of theta activity during LH ICS is presented in Figure 4. With respect to this figure, a criticism could be raised of the percentage power estimate during no ICS since it was sampled only at the start of the training session rather than throughout the session as was the estimate during ICS. However, a visual inspection, comparing the amplitude of theta during the LH ICS interval with the amplitude of theta occurring just before and after the ICS interval, confirmed the attenuation effect (Fig. 2A-C).

Several researchers have suggested that hippocampal theta activity is a correlate of motor activity (Paxinos & Bindra, 1970; Vanderwolf, 1969a, 1969b). Vanderwolf (1967, 1968, 1969a, 1969b) observed that hippocampal theta waves accompanied voluntary phasic skeletal movements, such as running and bar pressing in the rat. Desynchrony (large amplitude, slow, irregular waves) was found to accompany voluntary skeletal immobility (i.e., a rat clinging to legs by forepaws, Vanderwolf, 1969a). Similarly, desynchrony accompanied involuntary species-specific (consummatory) responses involving phasic skeletal movements, such as grooming, eating, and drinking. A second type of desynchrony (small amplitude, slow, irregular waves), lasting only 1-2 seconds, was found to accompany abrupt halts in ongoing behavior (i.e., a running gerbil abruptly halting to a sharp whistle). A somewhat different motor activity hypothesis was suggested by Paxinos and

Bindra (1970). These researchers stimulated the LH in rats and recorded hippocampal activity under two conditions. Continuous LH stimulation in nonconditioned rats resulted in locomotor exploration and was accompanied by theta activity. Continuous LH stimulation in rats operantly shaped to remain immobile for ICS was accompanied by desynchrony (large amplitude, slow, irregular waves). Paxinos and Bindra suggested that theta activity was a correlate of any large, continuous movements and desynchrony was a correlate of immobility and small, discrete movements. In order to demonstrate that voluntary movement was not sufficient for theta activity, Paxinos and Bindra reinforced grooming movements with ICS, resulting in a substantial increase in incidence of observed grooming behavior. However, a comparison of hippocampal records during spontaneous grooming (involuntary) and during ICS contingent grooming (presumably a voluntary movement) showed no detectable difference in the incidence of theta rhythm.

In order to study the more specific relationships of theta activity to voluntary skeletal movement, Vanderwolf (1969a) measured the frequency of theta prior to a conditioned avoidance response. The S was required to jump eleven inches to a platform to avoid shock. Except for slight movements of the head and tensing of the body, the response was always preceded by a period of immobility. Theta activity was continuously present during this immobile period and also during the sudden thrust of the hind legs during the performance of the response. The theta activity had a frequency of 6-7 Hz when it first

appeared, but increased regularly to a peak of 8-12 Hz just before the jump. These findings suggested to Vanderwolf that theta frequency is related to the temporal occurrence of the response. Paxinos and Bindra took exception with Vanderwolf's suggestion that theta precedes a response. Paxinos and Bindra (1970) placed electrodes in the musculature of the hind limb of rats. Theta activity was simultaneous with the EMG and overt movements. Paxinos and Bindra suggested that the theta preceding a response in Vanderwolf's study may be due to an experimental artifact; a time lag occurred between E's observation of the response and E's notation of the response on the record of hippocampal activity.

In addition to his suggestion that theta frequency was related to the temporal occurrence of the response, Vanderwolf (1969a, 1969b) also suggested that theta amplitude was related to the gross amount of concurrent motor activity. As further evidence that theta frequency and theta amplitude were the result of independent mechanisms, Vanderwolf cited his finding that correlations between frequency and amplitude in three rats were insignificant. The insignificant correlations in the present study between the frequency of theta peak and percentage of power of that peak during LH continuous and self stimulation and during DT stimulation confirm Vanderwolf's finding. However, Vanderwolf's own data (1969b) appear to suggest that a correlation should exist. He reported that the small amplitude theta present during small overt movements, such as paw manipulation of food or head turning, was of a

lower mean frequency than the large amplitude theta accompanying major movements such as walking or rearing. A possible reason for the lack of correlation is the observation by Vanderwolf (1969b) that, regardless of size of movement, the initiation of the movement is accompanied by higher frequency theta of approximately the same amplitude as the lower frequency theta accompanying the continuation of the movement. Thus, in comparing movements of varying size, the amplitude of a specific theta frequency may vary widely, depending upon whether the specific frequency occurred at the onset of a small motor movement or during the continuation of a large motor movement. Since the present study and the study by Vanderwolf (1969a) did not control for the temporal relation between the theta sampled and the behavioral response, these changes in theta frequency over time may have obscured any correlation between frequency and amplitude that might exist.

The effects of LH stimulation on hippocampal activity in the present study can best be explained in terms of a motor activity hypothesis (Paxinos & Bindra, 1970; Vanderwolf, 1969a, 1969b, 1971). First, whenever locomotor exploration was observed, in response to LH stimulation, the accompanying hippocampal response consisted of theta activity. In addition, small amounts of locomotor exploration were accompanied by less theta (amplitude) than grosser movements. When continuous LH stimulation did not elicit locomotor exploration, the concomitant hippocampal activity was desynchronous (large amplitude, slow, irregular waves). Second, if LH onset elicited freezing behavior

initially, followed by locomotor exploration, the accompanying hippocampal activity consisted initially of attenuated slow wave activity followed by large amplitude theta waves. Third, the smaller amplitude theta usually observed during LH self stimulation training is consistent with the observations of Vanderwolf and Wishaw (1969) and Bennett and Gottfried (1970). Vanderwolf and Wishaw found that theta activity during bar pressing in rats was reduced in amplitude as the rat's behavior changed from walking and rearing to regular bar pressing. Bennett and Gottfried found very little theta activity in cats bar pressing for milk on a DRL-20 sec. schedule. Although low amplitude theta usually accompanied LH self stimulation bar pressing in the present study, large amplitude theta activity or desynchronous activity were also observed. The behavioral and hippocampal activity correlates observed by Vanderwolf and Wishaw during bar pressing suggest that the variance in hippocampal activity during LH bar pressing in the present study was due to the variance in motor activity observed. The discrepancy between the present study and the studies by Kramis and Routtenberg (1969) and Pond and Schwartzbaum (1970) regarding hippocampal activity during bar pressing for LH ICS may also be due to differences in motor activity. Unfortunately, systematic observations of motor activity during LH self stimulation were not undertaken either in the present study or in those of Kramis and Routtenberg and Pond and Schwartzbaum.

The effects of DT stimulation on hippocampal activity can in the present study also be explained in terms of a motor activity hypothesis.

The 0.5 sec. trains of DT ICS, repeated once a second, elicited a burst of running which was terminated in the 0.5 sec. post-stimulatory interval. The ICS interval always contained fast wave theta (8-11 Hz) while the post-stimulatory interval always contained slow wave theta (6-9 Hz).

The positive correlations between theta frequency and intensity of ICS during LH and DT stimulation in the present study confirm the findings of other researchers (Kramis & Routtenberg, 1969; Pond & Schwartzbaum, 1970; Routtenberg & Kramis, 1968). It is possible that the positive correlations are due to the higher intensity ICS eliciting responses with shorter latencies from stimulation onset. This interpretation would be consistent with Vanderwolf's hypothesis that theta frequency is related to the temporal occurrence of the response. However, it is also possible that the positive correlations were due to higher ICS intensities eliciting grosser overt movements. Evidence for the latter interpretation was not found in the LH stimulation data; once stimulation was sufficient to elicit locomotor exploration, further increases in intensity did not appear to change the magnitude of the exploratory response. However, both the present study and the study by Routtenberg and Kramis (1968) found evidence to support the latter hypothesis in the DT stimulation data. Both studies observed a direct relationship between the magnitude of the behavioral response elicited by DT stimulation and the frequency of the concomitant theta activity.

A simple motor activity hypothesis cannot account for the presence of hippocampal theta during threshold levels of DT stimulation and the presence of either hippocampal theta or desynchrony during threshold levels of LH stimulation. Threshold levels of DT stimulation often elicited a pause in ongoing motor activity, with S's head raised and ears pricked, which was always accompanied by theta activity. Although threshold levels of LH stimulation elicited the same type of behavioral response, the accompanying hippocampal activity was, at times, synchronous, and, at other times, desynchronous. Similarly, the orienting hypothesis (Grastyán et al. 1959), which equates theta activity with overt orienting movements, would also have difficulty explaining the presence of desynchrony during LH elicited orienting behavior. However, this latter finding does not pose a problem for either the motor activity or orienting hypothesis if one assumes that the orienting behavior observed during threshold levels of DT and LH stimulation was not always the same. At higher ICS intensities, stimulation of the same LH site elicited, on some occasions, only locomotor exploration, and on other occasions, locomotor exploration preceded by an abrupt halting or freezing behavior. Dorsal tegmentum stimulation never elicited freezing behavior. Similar freezing behavior may have occurred occasionally at threshold levels of LH stimulation as well, but with reduced ICS intensity, the freezing response may have been reduced enough to make it indistinguishable from a delayed orienting response.

The arousal hypothesis (Bremner, 1964) would have difficulty explaining the desynchrony during threshold levels of LH stimulation and the desynchrony during higher levels of LH stimulation which accompanies freezing behavior. Bremner's arousal hypothesis correlates theta activity with centrally initiated attention or arousal. It is not clear why stimulation of the same LH site, at constant intensities, would on one occasion, initiate arousal, accompanied by theta, and, on another occasion, fail to initiate arousal (accompanied by desynchrony). Furthermore, it seems likely that an animal would be aroused during either freezing behavior or locomotor exploration.

References

- Adey, W. R., Dunlop, C. W., & Hendrix, C. E. Hippocampal slow waves, distribution and phase relationships in the course of approach learning. Archives of Neurology, 1960, 3, 74-90.
- Adey, W. R., Dunlop, C. W., & Sunderland, S. A survey of rhinencephalic interconnections with the brainstem. Journal of Comparative Neurology, 1958, 110, 173-204.
- Andersen, P., Brooks, C. Mc., & Eccles, J. C. Electrical responses of the ventrobasal nucleus of the thalamus. In W. Bargmann & J. P. Schadé (Ed.), Progress in brain research. Vol. 5. Lectures on diencephalon. Amsterdam: Elsevier, 1964.
- Andersen, P., & Eccles, J. C. Inhibitory phasing of neuronal discharge. Nature, London, 1962, 196, 645-647.
- Andersen, P., & Lømo, T. Mode of control of hippocampal pyramidal cell discharges. In R. E. Whalen, R. F. Thompson, M. M. Verzeano, & N. M. Weinberger (Ed.), The neural control of behavior. New York: Academic Press, 1970.
- Ball, G. G., & Grey, J. A. Septal self stimulation and hippocampal activity. Physiology and Behavior, 1971, 6, 547-550.
- Bennett, T. L., & Gottfried, J. Hippocampal theta activity and response inhibition. Electroencephalography and Clinical Neurophysiology, 1970, 29, 196-200.
- Blackman, R. B., & Tukey, J. W. The measurement of power spectra. New York: Dover, 1959.
- Bremner, F. J. Hippocampal activity during avoidance behavior in the rat. Journal of Comparative and Physiological Psychology, 1964, 58, 16-22.
- Dixon, W. J. Biomedical computer programs. Los Angeles, California: University of California Press, 1970.
- Douglas, R. Hippocampus and behavior. Psychological Bulletin, 1967, 67, 416-442.
- Edwards, A. L. Experimental design in psychological research. New York: Holt, Rinehart and Winston, 1963.
- Fujita, Y., & Sato, T. Intracellular records from hippocampal pyramidal cells in rabbits during theta-rhythm activity. Journal of Neurophysiology, 1964, 27, 1011-1025.

- Gerard, R. W., Marshall, W. H., & Saul, L. J. Electrical activity of the cat's brain. Archives of Neurological Psychiatry, 1936, 36, 675-738.
- Grastyán, E., Karmos, G., Vereczkey, L., & Kellenyi, L. The hippocampal electrical correlates of the homeostatic regulation of motivation. Electroencephalography and Clinical Neurophysiology, 1966, 21, 34-53.
- Grastyán, E., Karmos, G., Vereczkey, L., Martin, J., & Kellenyi, L. Hypothalamic motivational processes as reflected by their hippocampal electrical correlates. Science, 1965, 149, 91-93.
- Grastyán, E., Lissak, K., Madarasz, I., & Donhoffer, H. Hippocampal electrical activity during the development of conditioned reflexes. Electroencephalography and Clinical Neurophysiology, 1959, 11, 409-430.
- Green, J. D. The hippocampus. Physiological Review, 1964, 44, 561-608.
- Green, J. D., & Arduini, A. Rhinencephalic responses to afferent stimulus. Nineteenth International Physiological Congressional Abstracts, 1953, 409-410.
- Green, J. D., & Arduini, A. Hippocampal electrical activity in arousal. Journal of Neurophysiology, 1954, 17, 533-577.
- Heath, R. G. Studies on the function of the temporal lobe; section of the fornix. Transactions of the American Neurological Association (New York), 1951, 76, 238-239.
- Hendrickson, Carolyn, W., Kimble, R. J., & Kimble, D. P. Hippocampal lesions and the orienting response. Journal of Comparative and Physiological Psychology, 1969, 67, 220-227.
- Herrick, C. J. The functions of the olfactory parts of the cortex. Proceedings of the National Academy of Science of the United States, 1933, 19, 7-14.
- Holmes, J. E., & Adey, W. R. Electrical activity of the entorhinal cortex during conditioned behavior. American Journal of Physiology, 1960, 199, 741-744.
- Isaacson, R. L., Douglas, R. J., & Moore, R. Y. The effect of radical hippocampal ablation on acquisition of avoidance response. Journal of Comparative and Physiological Psychology, 1961, 54, 625-628.

- Ito, M. Hippocampal electrical correlates of self stimulation in the rat. Electroencephalography and Clinical Neurophysiology, 1966, 21, 261-268.
- Jung, R., & Kornmüller, A. E. Eine Methodik der Ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. Archives of Psychiatry, 1938, 109, 1-30.
- Kimble, D. P. Hippocampus and internal inhibition. Psychological Bulletin, 1968, 70, 285-295.
- Klüver, H., & Bucy, P. C. "Psychic blindness" and other symptoms following bilateral temporal lobectomy in Rhesus monkey. American Journal of Physiology, 1937, 119, 352-353.
- König, J. R. R., & Klippel, R. A. The rat brain. Baltimore: Williams and Wilkins, 1963.
- Kramis, R. C., & Routtenberg, A. Rewarding brain stimulation, hippocampal activity and footstomping in the gerbil. Physiology and Behavior, 1969, 4, 7-11.
- Liberson, W. T., & Akert, K. Observations on the electrical activity, of the hippocampus, thalamus, striatum, and cortex under resting conditions and during experimental seizure states in guinea pigs. Electroencephalography and Clinical Neurophysiology, 1953, 5, 320. 320.
- Mundl, W. J. An improved swivel for recording from behaving subjects. Electroencephalography and Clinical Neurophysiology, 1967, 23, 483-485.
- Nauta, W. J. H. An experimental study of the fornix system in the rat. Journal of Comparative Neurology, 1956, 104, 247-270.
- Olds, J., & Olds, M. Drives, rewards, and the brain. New directions in psychology II. New York: Holt, Rinehart, and Winston, 1964.
- Papez, J. W. A proposed mechanism of emotion. Archives of Neurological Psychiatry, 1937, 38, 727-743.
- Paxinos, G., & Bindra, D. Rewarding intracranial stimulation, movement and the hippocampal theta rhythm. Physiology and Behavior, 1970, 5, 227-231.
- Penfield, W., & Milner, B. Memory deficit produced by bilateral lesions in the hippocampal zone. A.M.A. Archives of Neurology and Psychiatry, 1958, 79, 475-497.

- Petsche, H., Gogolak, G., & van Zwieten, P. A. Rhythmicity of septal cell discharges at various levels of reticular excitation. Electroencephalography and Clinical Neurophysiology, 1965, 19, 25-33.
- Petsche, H., Stumpf, C., & Gogolak, G. Significance of the rabbit's septum as a relay station between the midbrain and the hippocampus. I. The control of hippocampus arousal activity by septum cells. Electroencephalography and Clinical Neurophysiology, 1962, 14, 202-211.
- Pond, F. J., & Schwartzbaum, J. S. Hippocampal electrical activity evoked by rewarding and aversive brain stimulation in rats. Communications in Behavioral Biology, 1970, 173, 001-015.
- Raisman, G., Cowan, W. M., & Powell, T. P. S. The extrinsic afferent, commissural and association fibers of the hippocampus. Brain, 1965, 88, 963-996.
- Ramon y Cajal, S. Histologic du systeme nerveux de l'homme et es vertebra. Paris: A. Maloine, 1909.
- Renshaw, B. A., Forbes, A., & Morrison, B. R. Activity of the isocortex and hippocampus: electrical studies with microelectrodes. Journal of Neurophysiology, 1940, 3, 74-105.
- Rose, M. Die sog. Riechrinde beim menchen und beim affen. Journal of Psychological Neurology, Leipzig, 1927, 34, 261-401.
- Routtenberg, A. Pentobarbital anesthesia of albino rats. Journal of the Experimental Analysis of Behavior. 1968, 11, 52.
- Routtenberg, A., & Kramis, R. C. Hippocampal correlates of aversive mid-brain stimulation. Science, 1968, 160, 1363-1365.
- Scoville, W. B., & Milner, B. Loss of recent memory after bilateral hippocampal lesions. Journal of Neurosurgery and Psychiatry, 1957, 20, 11-21.
- Spencer, W. A., & Kandel, E. R. Hippocampal neuron responses to selective activation of recurrent collaterals of hippocampofugal axons. Experimental Neurology, 1961, 4, 149-161.
- Stepien, L., & Sierpinski, S. Impairment of recent memory after temporal lesions in man. Neuropsychologia, 1964, 2, 291-303.
- Stumpf, C. The fast component in the electrical activity of rabbits' hippocampus. Electroencephalography and Clinical Neurophysiology, 1965, 18, 477-486.

- Torii, S. Two types of pattern of hippocampal electrical activity induced by stimulation of hypothalamus and surrounding parts of rabbit's brain. Japanese Journal of Physiology, 1961, 11, 147-157.
- Vanderwolf, C. H. Behavioral correlates of "theta" waves. Proceed. Canad. Fed. Biol. Soc., 1967, 10, 41-42.
- Vanderwolf, C. H. Hippocampal electrical activity and voluntary movement in the rat. Technical Report Number 17, Department of Psychology, McMaster University, 1968.
- Vanderwolf, C. H. Hippocampal electrical activity and voluntary movement in the rat. Electroencephalography and Clinical Neurophysiology, 1969a, 26, 407-418.
- Vanderwolf, C. H. Limbic-diencephalic relations in the higher level control of movement. Research Bulletin No. 126, London, Canada: University of Western Ontario, 1969b.
- Vanderwolf, C. H. Limbic-diencephalic mechanisms of voluntary movement. Psychological Review, 1971, 78, 83-113.
- Vanderwolf, C. H., & Wishaw, I. Q. Is hippocampal electrical activity altered by training? Paper presented at the meeting of the Psychonomic Society, St. Louis, Missouri, November, 1969.

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